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Differential Effects of Two Serotonin Depletors on Apomorphine-Induced Behaviors

by

© Hau Lin Chow

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
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Date..April 22, 1983.........

Abstract

Behaviors of adult male rats (120, Sprague Dawley) in open field alone and social conditions were used to investigate the differential effects of two 5-HT depletors, *p*-chlorophenylalanine (*p*-CPA) and *p*-chloroamphetamine (*p*-CA), on Apomorphine (Apo)-induced behavioral syndrome. In addition to the hyperactivity and stereotypy components, preliminary studies indicated that the Apo behavioral effect might include a component of hyperreactivity. Apo acts centrally as a dopaminergic agonist, but it secondarily also activates the 5-HT system. It was hypothesized that there would be fewer number of functional 5-HT neurons in a *p*-CA pretreated animal than in a *p*-CPA pretreated one because *p*-CA depletes 5-HT by neuronal destruction while *p*-CPA depletes 5-HT by blockage of the enzyme tryptophan hydroxylase. Since Apo seems to activate the 5-HT system via intact 5-HT neurons, an Apo challenge would be less effective in activating the 5-HT system in a *p*-CA pretreated animal than Apo could in a *p*-CPA treated one. It was predicted that although both *p*-CPA and *p*-CA pretreatments would potentiate all aspects of Apo-induced behavior, *p*-CA pretreatment would show greater potentiation than would *p*-CPA. These predictions were partially confirmed. *p*-CPA pretreatment potentiated aspects of stereotypy without altering either the hyperactivity or the hyperreactivity effects of the Apo. *p*-CA pretreatment, on the other hand, potentiated both Apo-induced hyperactivity and

hyperreactivity but it also suppressed aspects of stereotypy. The possible underlying causes for this differential potentiation were discussed, arriving at the conclusion that there might be a differential neuroanatomical depletion pattern of 5-HT by *p*-CPA and *p*-CA.

The study also presented a more comprehensive paradigm for the assessment of the Apo behavioral effect - focusing on detailed logging of behaviors using exhaustive categories, obtaining more than one dependent measure for each behavior and testing the animals in isolation and in pairs. This paradigm comfirmed both the hyperactivity and stereotypy components of the Apo behavioral effect as well as suggested that there might be a component of hyperreactivity.

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I. INTRODUCTION

A. Purpose

One of the standard approaches to studying the behavioral effects of a neurochemical system is to examine the effects on behavior of specific depletors of that neurochemical and to compare the profile to that of the normal intact system. Serotonin (5-hydroxytryptamine or 5-HT) has been extensively studied in this manner. Two commonly used depletors of 5-HT are *para*-chlorophenylalanine (*p*-CPA) and *para*-chloroamphetamine (*p*-CA). The purpose of this experiment is to differentiate behaviorally the long term effects - after three days - of these two depletors by studying their actions on apomorphine-induced hyperactivity and stereotypy. Both depletors have been used experimentally in humans. *p*-CPA has been used in the treatment of patients with carcinoid syndrome - which produces excess amounts of 5-HT (Sjoerdsma, Lovenberg, Engelman, Carpenter, Wyatt, & Gessa, 1970). *p*-CA has been shown to have antidepressant properties in man (Van Praag & Korf, 1973). Thus information concerning the behavioral differences between these two 5-HT depletors would be of importance for any further clinical applications of the two depletors.

B. p-CPA, p-CA - Biochemical Effects

At three days, both *p*-CPA and *p*-CA are potent depletors of 5-HT in the rat, but, their mechanisms of action are quite different. One, *p*-CPA (single dose) causes depletion via inhibition of tryptophan hydroxylase, the rate limiting enzyme in the synthesis of 5-HT (Koe & Weissman, 1966). *p*-CA (single dose), on the other hand, causes depletion via selective destruction of 5-HT neurons (Harvey, McMaster, & Yunger, 1975). Two, whereas *p*-CPA induces depletion of 5-HT both in the brain and in other organs of the body (Koe & Weissman, 1966), *p*-CA induces depletion only in the brain (Kohler, Ross, Srebro, & Ogren, 1978). In addition, 5-HT is also differentially depleted in different regions of the brain by *p*-CA (Dewhurst & McKim 1980; Kohler et al., 1978). Three, the 5-HT system can recover from the depletion effect of *p*-CPA via synthesis of new tryptophan hydroxylase enzyme (Jequier, Lovenberg, & Sjoerdsma, 1972). However, the 5-HT level is still depressed four months after a single dose of *p*-CA (Sanders-Bush, Bushing, & Sulser, 1972).

C. p-CPA, p-CA - Behavioral Effects

Whereas biochemical studies have revealed differences between the two depletors, behavioral studies have revealed similarities. These studies can be categorized into three major areas : those dealing with overall activity level, those dealing with avoidance learning, and those dealing with interactive behaviors. For overall activity, a single dose of *p*-CPA (300mg/kg; -3days) increases both wheel running and stabilimeter activities (Fibiger & Campbell, 1971). A single dose of *p*-CA (5mg/kg; -3days) also increases stabilimeter activity (Messing, Phebus, Fisher, & Lytle, 1976). In addition, pretreatment with a single dose of *p*-CPA (316mg/kg; -3days) potentiates apomorphine-induced stabilimeter activity (Grabowska, Antkiewicz, Maj, & Michaluk, 1973). Pretreatment with multiple doses of *p*-CA (5 daily doses of 2mg/kg; tested 3 days after the last dose) also potentiates apomorphine-induced photobeam activity (Grabowska & Michaluk, 1974). In contrast to these measures, multiple doses of *p*-CPA (3 daily doses of 100mg/kg; tested between 1 and 5 days after the last dose) decrease the number of squares crossed in an open field paradigm (Vorhees, 1979). Likewise, multiple doses of *p*-CA (2 daily doses of 5mg/kg; tested 7 days after the last dose) also decrease open field square crossings (Kohler et al., 1978).

For avoidance learning, the general effect of both *p*-CPA and *p*-CA is one of facilitation. Thus, multiple doses of *p*-CPA (3 daily doses of 100mg/kg; tested between 1 and 5 days after the last dose) facilitate Y-maze avoidance learning (Vorhees, 1979). Multiple doses of *p*-CA (3 daily doses of 5 mg/kg; tested between 1 and 15 days after the last dose) also facilitate Y-maze avoidance learning plus increase the intertrial activity (Vorhees, Schaefer, & Barrett, 1975). For Sidman bar-press, a single dose of *p*-CPA

(300mg/kg; tested between 1 and 5 days after administration) facilitates the response rate as well as showing a decrease in the number of shocks received (Tanaka, Yoh, & Takaori, 1972). Likewise, a single dose of *p*-CA (5mg/kg) also facilitates the bar-press response rate - but only during the first 24-hour postinjection period (Steranka, Barrett, & Sanders-Bush, 1977). For jump avoidance, multiple doses of *p*-CPA (3 daily doses of 100mg/kg; tested 24 hours after the last dose) facilitate acquisition of the jump response (Tenen, 1967). In a somewhat similar task, a single dose of *p*-CA (6mg/kg; tested between 1 and 7 days after the last dose) facilitates the acquisition of the shuttle-box avoidance response (Vorhees, 1979).

As with avoidance learning, the effect of both *p*-CPA and *p*-CA on interactive behaviors is also one of facilitation. For social interactions, multiple doses of *p*-CA (3 daily doses of 8mg/kg; tested immediately after the last dose) elicit "social bizarre behavior" in groups of similarily drugged rats in response to sound or handling (Korf & Kuiper, 1971). This is characterized by pairs of animals standing on their hindlegs, facing each other with their mouths close together for extended periods of time. No similar experiment has been done with *p*-CPA. For sexual interactions, both drugs facilitate male sexual behaviors in male and female rats. Thus, multiple doses of *p*-CPA (4 daily doses of 100mg/kg; tested 13 hours after the last dose) enhance masculine sexual activities such as the frequency of attempted mounting in groups of similarily drugged male rats (Tagliamonte, Tagliamonte, Gessa, & Brodie, 1969). Likewise, multiple doses of *p*-CA (2 daily doses of 10mg/kg; tested between 5 and 7 days after the last dose) increase the frequency of ejaculation in castrated male rats in the presence of a receptive female rat (Sodersten, Berge, & Hole, 1978). In the same study, the same dosage of *p*-CA also enhances the frequency of attempted mounting in ovariectomized female rats when paired with a normal female. For mouse-killing behavior, extremely high multiple doses of *p*-CPA (3 daily doses of 300mg/kg; tested 3 days after the last dose) induce muricide in previously non-killer rats (Miczek, Altman, Appel, & Boggan, 1975). However, in the same study, neither a smaller dose of *p*-CPA (3 daily doses of 100mg/kg), nor *p*-CA (3 daily doses of 3.5mg/kg) reliably produced muricide.

In summary, both *p*-CPA and *p*-CA increase stabilimeter activity but decrease open field activity. Both drugs facilitate acquisition of avoidance learning under various paradigms. Both also increase male sexual activities in both male- and female-treated rats. Finally, neither increases muricidal behavior at moderate dosages.

D. Critique of Behavioral Studies

One conclusion that can be drawn from the foregoing studies is that there is no difference in the behavioral effects of these two 5-HT depletors. However, two major issues of concern need to be addressed before that conclusion can be drawn decisively : namely, the use of multiple injection schedules in most of the studies, and the focus of the paradigms on very specific behaviors in all of the studies. Multiple injection schedules not only confound the short-term and the long-term effects of the drug used, they fail to address the problematic possibility that the animal's system would not react in the same way between the initial and subsequent exposures to the same drug (Steranka, Sanders-Bush, & Barrett, 1977). A single injection schedule would circumvent these difficulties. The focus on specific behaviors (such as muricide, attempted mounting), although valid under the paradigms used, does neglect a large portion of the animal's repertoire of behaviors. This neglect may be one of the reasons why the above studies have been unable to detect the differences between *p*-CPA and *p*-CA effects. A paradigm that allows sampling of a wide range of behaviors and systematic collection of a detailed log of these behaviors may be what is needed to detect the subtle differences between *p*-CPA and *p*-CA.

In addition to these methodological changes (that is, single injection schedule, and detailed behavioral log), one could maximize the subtle differences between *p*-CPA and *p*-CA by incorporating into the experimental design a biochemical challenge to the 5-HT system. Since in the *p*-CPA and *p*-CA pretreated animals, the 5-HT system is only marginally operative, such a challenge would severely stress the animals' coping mechanisms that are dependent on the integrity of the 5-HT system. The stress load may be what is needed to reveal the subtle differences between the two 5-HT depletors. Thus, one strategy is to exploit the homeostatic balance between the various neurotransmitters in the central nervous system. This principle of homeostatic balance states that increased activation of neurotransmitter systems that produce behavioral excitation is paralleled by a concomitant increase in activation of systems that produce behavioral inhibition. Since the presence of 5-HT produces a general behavioral inhibition (Seiden & Dykstra, 1977, chap.4), interventions that are excitatory in nature should evoke a complementary activation of the 5-HT system. The dopamine (DA) system, when activated, produces behavioral arousal (Seiden & Dykstra, 1977, chap.5). Therefore, interventions that activate the DA system should also activate the 5-HT system as well. A biochemical activation of the DA system can be achieved by using apomorphine - a DA agonist (Ernst, 1967).

Another strategy is to exploit the relationship between 5-HT and stress : stress has been shown to increase 5-HT utilization. Thus, intermittent grid shock produces an increase in 5-hydroxyindoleactic acid (5-HIAA) level, the metabolite of 5-HT (Bliss, Ailion, & Zwanziger, 1968). Likewise, footshock has been found to markedly increase synthesis of radioactively labelled 5-HT (Thierry, Fekete, & Glowinski, 1968). Thus situations that induce stress should further tax the already depleted 5-HT system in the *p*-CPA and *p*-CA pretreated animals. Open field activity in a novel environment and social interactions with a novel partner are also examples of stressful situations (File & Hyde, 1978). Simultaneous exposure to a novel environment and to a novel partner has been shown to increase plasma corticosterone level. This change in plasma corticosterone level has been considered a measure of the reaction of the hypothalamo-pituitary-adrenal system to stress (File & Peet, 1980). In addition, lesion of the dorsal raphe nucleus by 5,7-dihydroxytryptamine (a toxin specific for 5-HT neurons), has been shown to produce an anxiolytic profile in the open field similar to that seen in rats given benzodiazepines (File, Hyde, & McLeod, 1979). Thus, although exposure to the open field and social interaction with a novel partner are relatively mild stressors as compared to other stressors such as electric shock (File & Hyde, 1978), these two situations are capable of inducing stress related physiological changes as well as eliciting the role of 5-HT system in the stress reaction. Furthermore, the open field and social interactions are not only more naturalistic procedures (File & Hyde, 1978), but they also increase the range of possible behaviors that can be elicited and sampled.

In summary, with the methodological changes (single injection schedule, wider range of behaviors sampled, and detailed behavioral log) as well as the use of biochemical (DA) and environmental (open field, social interactions) stressors, the behavioral correlates of the subtle biochemical differences between *p*-CPA and *p*-CA may become detectable.

E. Biochemical Stressor

Apomorphine - Biochemical Effects

Apomorphine (Apo) inhibits both DA turnover (Anden, Robenson, Fuxe, & Hakfelt, 1967; Nyback, Schubert, & Sedvall, 1970) and DA synthesis (Roos, 1969). These actions appear to be mediated by direct stimulation of brain DA postsynaptic receptors (Anden et al.,1967; Ernst, 1967; Roos, 1969). Apo also has been shown to increase whole brain levels of 5-HT and its metabolite, 5-HIAA (Grabowska et al., 1973; Scheel-Kruger & Hasselager, 1974). In addition, the turnover rate of 5-HT seems to be increased by Apo (Grabowska, 1975). These actions of Apo on the 5-HT system can be blocked with various butyrophenones, DA receptor blockers, (Grabowska et al., 1973) or by a transection separating the raphe region (containing the serotonergic cell bodies) from the diencephalon (containing the dopaminergic cell bodies) (Grabowska, Przewlocki, & Smialowska, 1976). These results suggest that the Apo effects on 5-HT are not due to a direct effect on the 5-HT neurons but rather due to a secondary effect of central DA receptor activation by Apo (Grabowska et al., 1973; Grabowska et al., 1976). In addition, 5-HT neurons have been found to co-exist with DA neurons in the striatum and mesolimbic structures (Saavedra, Brownstein, & Palkovits, 1974). This provides the anatomical basis for the 5-HT - Apo interactions.

F. Apo - Behavioral Effects and Critique of Studies

The behavioral effects of Apo in an intact animal have not been studied satisfactorily. Although there is a general consensus that Apo produces periods of heightened activity level as well as stereotypic activities, the exact dosage and time course relationships have been disputed (Ljungberg & Ungerstedt, 1977a). This dispute may be due to the nature of the measuring instruments used (Fray, Sahakian, Robbins, Koob, & Iversen, 1980).

Activity level has been most commonly measured as the number of photobeam interruptions over a period of time (Meyerson & Hoglund, 1981). One criticism of this measurement is that it is only sensitive to gross movements such as locomotion and rearing; finer ones such as sniffing, licking, and grooming are not detected (Grabowska & Michaluk, 1974). In addition, an absolute increase or decrease of activity as measured by this method does not allow for further analysis of underlying causal mechanisms since changes in activity can be caused by many different factors. Thus, the frequency of photobeam interruptions may be the same for two different conditions (such as resting versus freezing behaviors), but the underlying neural control mechanisms may be very different (Meyerson & Hoglund, 1981). Furthermore, the measure of hyperactivity as defined by increased photobeam interruptions, is potentially confounded by reactivity contributing to the heightened activity level. That is, activity level could be altered indirectly by modifying the reactivity of an animal to its environment.

Degree of stereotypy has been assessed by using 4 to 6 point rating scales with interrupted sniffing and continous gnawing as signs of minimal and maximal stereotypy respectively (Costall & Naylor, 1973; Ernst, 1967; Sahakian, Robbins, Morgan, & Iversen, 1975). Several important arguments have been raised concerning the use of rating scales for this purpose (Fray et al., 1980; Ljungberg & Ungerstedt, 1977a). One, the rating scales assume that the transition of one behavior, example, sniffing, to the next, example, gnawing, represents the increasing intensity of a unified construct - stereotypy. In fact, sniffing and gnawing have been dissociated experimentally (Fray et al., 1980). Two, ratings generated from these scales are ordinal measures, therefore, the use of mean values and parametric statistics may not be appropriate. Three, the rater is asked not only to assess the occurrence of a particular behavior, such as sniffing, but also its intensity. This is both a demanding as well as a very subjective task. Four, rating scales focus on only sniffing and gnawing, thus they leave the majority of the animal's behavioral repertoire unassessed. Alternately, Fray et al.(1980), employing exhaustive behavioral categories, recorded the presence and absence of several key behaviors with no judgment of intensity. Thus, they were able to show that sniffing, licking, and gnawing all have different dosage thresholds and time courses.

Another methodological issue to be considered is the confusion between the operational definitions of the hyperactivity and stereotypy components of the Apo effect. A key criterion of increasing stereotypy, as defined by the rating scales, is a decrease in overall activity. All stereotypy scales have gnawing-at-one-location as the highest score. Since the definitions of hyperactivity and stereotypy are not in fact independent of each other, attempts to conceptually separate the two components in terms of underlying controlling mechanisms would not be appropriate. The concepts themselves are useful, but the operational definitions need to be refined.

Thus, in summary, the behavioral effects of Apo have not been studied satisfactorily in the majority of experiments reported, primarily due to the inadequacies of the commonly used measuring instruments and the operational definitions of the components of hyperactivity and stereotypy.

G. Localization of hyperactivity and stereotypy components

Studies of localization have been conducted using electrolesion, 6-hydroxydopamine (6-OHDA), and direct application of Apo or DA. The major structures of interest have been the caudate-putamen complex, the globus pallidus, the tuberculum olfactorium and the nucleus accumbens.

Results have not been entirely consistent, largely due to the proximity of the targeted structures as well as the striatal and mesolimbic DA pathways themselves. In addition, since these studies have used the same inadequate behavioral measures as those in studies of the Apo effects (discussed in the last section), this has likely also contributed to the lack of consistency in the results.

The mesolimbic pathway has been most often cited as playing a crucial role in the Apo-induced hyperactivity; however the exact structure involved has been disputed. Direct application of Apo into the nucleus accumbens results in either enhanced motor activity (as defined by photobeam interruptions)(Grabowska & Anden, 1976) or no change (Costall, Naylor, & Neumeyer, 1975a). However, direct application of DA to this structure does result in enhanced motor activity (Costall et al., 1975a; Pijnenburg & van Rossum, 1973). A 6-OHDA pretreatment to this structure also enhances the subsequent motor response to Apo application (Kelly, Seviour, & Iversen, 1975). However, the importance of the nucleus accumbens as the crucial site has been disputed. The tuberculum olfactorium has been cited as the alternate - or at least adjunct- candidate. This is because 6-OHDA lesions of the nucleus accumbens often damage the tuberculum olfactorium as well (Kelly et al., 1975). In addition, application of either Apo or DA to this structure have resulted in enhanced motor activity (Costall & Naylor, 1975; Pijnenburg, Honig, van der Heyden, & van Rossum, 1976). Thus the involvement of the tuberculum olfactorium in hyperactivity cannot be ruled out.

Whereas only the mesolimbic pathway has been implicated in the hyperactivity component, both striatal and mesolimbic structures have been cited as crucial for the stereotypy component. Direct application of Apo to the striatum or globus pallidus results in high stereotypy scores (biting, gnawing) (Ernst & Smelik, 1966; Grabowska & Anden, 1976). However, electrolesion of the tuberculum olfactorium, while sparing the overlaying striatum, abolishes subsequent Apo-induced stereotypy (McKenzie, 1972). Direct application of either DA or Apo to the tuberculum olfactorium also elicits stereotypic behaviors (Costall, Naylor & Neumeyer, 1975a; Costall, Naylor, & Neumeyer, 1975b).

In summary, the hyperactivity component of the Apo effect has been localized in the nucleus accumbens - tuberculum olfactorium area. However, the crucial area for the stereotypy component is less defined: the striatum, globus pallidus and tuberculum olfactorium have all been suspected.

H. Behavioral Interactions between Apo and 5-HT

A critical prequisite for this study is the investigation of the behavioral interactions between Apo and the intact 5-HT system. This has been commonly studied by manipulating 5-HT levels and then observing the effects on

Apo-induced hyperactivity and stereotypy.

In general, the effect of the presence of the 5-HT system on Apo-induced hyperactivity is behavioral suppression. Thus, a single dose of 5-HTP, a precursor of 5-HT, decreases Apo-induced hyperactivity while a single dose of *p*-CPA, a depletor, increases Apo-induced hyperactivity (Grabowska et al., 1973). Multiple doses of *p*-CA have also been found to have a similar potentiating effect on Apo-induced hyperactivity as that found from a single dose of *p*-CPA (Grabowska & Michaluk, 1974). Less directly, methysergide, a 5-HT antagonist, has been found to potentiate the Apo-induced kinetic effect in 6-OHDA-lesioned hypokinetic animals (Voith, 1980). This last study suggests that 5-HT has an inhibitory effect on locomotion induced by Apo. Thus, the general conclusion from all the above studies is that the presence of 5-HT suppresses Apo-induced hyperactivity.

The effect of the presence of the 5-HT system on Apo-induced stereotypy is not as definitive. Methysergide, multiple doses of *p*-CPA, and 5-HTP all fail to significantly alter the stereotypic scores obtained from rats injected with Apo (Baldessarini, Amatruda, Griffith, & Gerson, 1975; Rotrosen, Angrist, Wallach, & Gershon, 1972). However, Weiner, Goetz, and Klawans (1975) found that methysergide potentiates stereotypic activity in the guinea pig when subthreshold dosages of Apo are used. In the same study, they also found that 5-HTP raises the stereotypy threshold dosage of Apo.

In summary, there is good evidence for the suppressive effect of 5-HT on Apo-induced hyperactivity, but the nature of the 5-HT involvement in Apo-induced stereotypy is not as definitive.

I. Behavioral Stressors

Open field alone and social interaction

The selection of these two specific behavioral stressors (that is, exposure of animal to a novel open field as well as to a strange partner) serves three purposes. One, these stressors are more naturalistic. They provide a means of examining the effects of biochemical manipulations on ecologically valid representations of the rat's environment. Such ecological doses of stress vitiate disruptive treatments such as electric shock and food or water deprivation (File & Hyde, 1978). Two, the use of both behavioral conditions permit the expression of a wider range of behaviors. Three, the specific alternation of the two behavioral conditions provides a means of assessing degree of reactivity.

A non-drugged rat placed alone in a novel open field environment shows a characteristic pattern of behaviors (Beck & Chow, unpublished data). In the first 10 minutes, approximately 85% of the animal's time is spent in exploration: sniffing, locomoting, and rearing. The animal spends the rest of the time in self-grooming. Repeated exposure to the same environment results in a rapid habituation whereby increasing proportions of time are spent in self-grooming and being inactive.

A very different pattern of behavior can be elicited when another, non-drugged, rat is introduced into the same open field environment (Beck & Chow, unpublished data). During the first 10 minutes of exposure to this 'intruder rat', there is a strong facilitation of locomotion coupled by very strong suppressions of both sniffing and rearing of the 'resident rat'. Total exploration time is reduced to approximately 55% (from 85%). Approximately 40% of the resident rat's time is now spent in social interaction with the 'intruder rat'. There is minimal self-grooming or inactivity. Preliminary data indicates that this pattern of behavior is stable up to three repeated exposures in a period of 80 minutes.

The use of a non-drugged, rather than a similarily drugged, rat as a source of social stimulation for a experimentally-drugged rat serves two purposes. File & Pope(1974) found that there are more frequent changes from one behavior to another in pairs of rats where only one is drugged as compared with pairs where both are in the same drug state. Thus the use of a non-drugged partner helps to generate a overall higher frequency of behaviors. More importantly, the consistent use of a non-drugged rat as the source of social stimulation reduces the variance due to the interactions between drug states . It has been shown that there is an interaction between the effects of a drug and the dominance-submissiveness relationship between pairs of rats (Miczek, 1974). Thus to study interactive behavior in pairs of similarily drugged rats would obscure this interaction. Furthermore, while there is no difference between the behaviors of each individual rat in pairs of non-drugged rats in an open field situation, the behaviors generated are different from those of a non-drugged rat when paired with a drugged one in the same paradigm (McDonald & Heimstra, 1965). This is due to the comples nature of the interactions involved - each rat of the pair elicits behaviors from the other and reacts to behaviors generated by the other. Thus different behaviors can be elicited from the same experimental animal depending on the drug state of the partner provided. The consistent use of a non-drugged rat as the partner for the experimental drugged rat although cannot remove all the variance in this complex set of interactions, can reduce that part of the variance due to the non-drugged rat's reactions to behaviors of the experimental drugged rat.

In summary, the use of the alone and social interaction conditions in a open field environment - and especially in an alternating manner - as behavioral stressors has several advantages. These are more naturalistic situations. They provide the opportunity to elicit a wide range of behaviors. As well, the alternation of the two conditions provides the added opportunity to assess reactivity. Finally, the use of a non-drugged partner in the social interaction reduces the variance due to the interaction between the drug states of the two rats.

J. Summary of Experimental Design

The purpose of this experiment is to differentiate behaviorally the long-term effects - after three days - of *p*-CPA and *p*-CA, two 5-HT depletors, by studying their effects on the Apo-induced behavioral syndrome.

The design summarized below attempted to address some of the methodological issues raised about the current research of *p*-CPA, *p*-CA, and Apo effects, as well as to produce a paradigm that maximized the subtle differences between *p*-CPA and *p*-CA. The use of single injection shedule circumvented the problems associated with multiple injections. The use of both open field alone and social conditions circumvented the narrow focus of the previous studies. As well, they provided more stress to the already depleted 5-HT system (that is, they were the behavioral stressors). These two conditions also provided the opportunity to assess degree of reactivity and its possible interaction(s) with hyperactivity and stereotypy. The recording of the onset and offset of specific behaviors circumvented the inadequacies with the rating scales for stereotypy. This method of data collection also provided the opportunity to further analyze the phenomenon of hyperactivity.

II. EXPERIMENTAL HYPOTHESIS

A. Hypothesis

Apo administration to an intact animal causes a initial increase of 5-HT level by a higher turnover rate of 5-HT (Grabowska, 1975). This action seems to be the result of Apo's central activating effect on DA neurons. That is, the activation of DA neurons in turn activates 5-HT neurons. This sequence of events would suggest that intact 5-HT neurons are necessary for the Apo's effect of increased turnover of 5-HT. Since *p*-CA is toxic to 5-HT neurons (Harvey, et al., 1975), a *p*-CA pretreated animal would be expected to have fewer number of functional 5-HT neurons than a *p*-CPA pretreated animal, even though both animals might have a comparable level of 5-HT depletion. Thus, a Apo challenge to a *p*-CA pretreated animal would be less effective in activating the 5-HT system than Apo could in a *p*-CPA pretreated animal. This is the hypothesized biochemical differential reaction of *p*-CPA and *p*-CA to an Apo challenge. In addition, two dosages of both *p*-CPA and *p*-CA were used in order to study the effect of different levels of 5-HT depletion has on Apo-induced behaviors.

B. Expected Findings

Since the presence of 5-HT suppresses Apo-induced hyperactivity, pretreatment with either *p*-CPA or *p*-CA, both of which are 5-HT depletors, would be expected to potentiate this hyperactivity. Furthermore, there would be a differential potentiation : *p*-CA pretreatment would show a greater potentiation than *p*-CPA pretreatment. More specifically, this greater potentiation of the *p*-CA group would be expressed as faster rate of locomotion, higher frequency of bouts of locomotion with perhaps shorter bout duration. This heightened activity would have consequences on other competing responses such as resting and self-grooming. These would be expected to decrease in frequency and duration since more time is spent locomoting.

If the effect of this overall heightened activity of both *p*-CPA and *p*-CA pretreatments were caused by a heightened reactivity response, then both pretreatments would be expected to have a disrupted pattern of exploratory behavior and habituation in response to the open field alone and social interaction conditions. Habituation to the environment in the form of decreased overall activity would likely not occur, especially if the animal were fearful. Consequently, there would be less social interaction in the social situation (Eckman, Meltzer, & Latane, 1969). Again, the *p*-CA pretreatment would be expected to show a greater reactivity response.

The effect of either pretreatment on Apo-induced stereotypy is more difficult to predict as the current literature is not as definitive. If the effect of the presence of 5-HT were one of suppression as suggested by Weiner et al. (1975), then both pretreatments would be expected to potentiate the stereotypy. The potentiation could be one of shorter latency of onset, longer duration, or greater intensity of stereotypy. Furthermore, the *p*-CA pretreatment potentiation would be expected to be greater than that for *p*-CPA. However, if 5-HT does not play a modulating role, then neither *p*-CPA nor *p*-CA pretreatment would be expected to have any effect on Apo-induced stereotypy.

III. METHOD

A. Subjects

Adult male Sprague Dawley rats (120; Ellerslie Animal Farm, University of Alberta) weighing approximately 260-310 grams at the time of the first injection were used. The animals were randomly assigned to either the experimental (drugged) or the social stimulus (non-drugged) groups. The experimental group was further randomly divided into the six drug groups. All animals were used only once. The animals were individually housed and were maintained *ad libitum* on food and water. Room lighting was provided between 2100 and 0900 hours (reverse day-night), and a temperature of 19±2°C was maintained. The animals were brought in two weeks ahead of the time of behavioral testing to allow them to be adjusted to the reverse day-night cycle.

B. Apparatus

The test apparatus was a black wooden box (55x66x64cm) with 30 squares (11x11cm) marked off on the floor. Illumination of the test room was provided by a 45-watt red light suspended approximately 120 cm above the floor of the test apparatus. A one-way mirror was positioned at an angle of 60° relative to the top of the test apparatus in order to provide an unobstructed view of the animals by the coder as well as to prevent the animal from seeing the coder. A microcomputer was used to record the behaviors.

C. Drugs and Dosage

The drugs used were: p-chlorophenylalanine methyl ester hydrochloride (Sigma), p-chloroamphetamine hydrochloride (Sigma), and apomorphine hydrochloride (Sigma). All drugs were dissolved in 0.9% saline immediately prior to being used.

p-CPA, *p*-CA and all saline injections were administered intraperitoneally (ip). Apo injections were administered subcutaneously (sc) in the right flank area. The first injection was given 3 days prior to behavioral testing and the second injection was given 5 minutes prior to behavioral testing.

The drug groups were:

group	first injection	second injection
1	0.9% saline(2ml/kg)	, 0.9% saline(2ml/kg)
2	0.9% saline(2ml/kg)	, Apo(5mg/kg)
3	*p*-CPA(400mg/kg)	, Apo(5mg/kg)
4	*p*-CPA(250mg/kg)	, Apo(5mg/kg)
5	*p*-CA(10.4mg/kg)	, Apo(5mg/kg)
6	*p*-CA(6.4mg/kg)	, Apo(5mg/kg)

Each group consisted of 10 experimental (injected) and 10 social stimuli (non-injected) animals.

The dosages for groups 3 and 5 were equated for level of whole brain 5-HT depletion (87%) at 3 days. Likewise, the dosages for groups 4 and 6 were also equated for level of whole brain 5-HT depletion (68%) at 3 days.

D. Procedure

Behavioral testing occurred during the first half of the animal's dark cycle between 0930 and 1600 hours. Three days prior to behavioral testing, each experimental animal was weighed, administered the first injection and immediately returned to its home cage. At the day of testing, each animal was re-weighed, administered the second injection and immediately placed in the test apparatus. Behavioral testing began after a 5-minute adaptation to the test box. Dark marks were placed on the head region of the social stimulus animals in order to distinguish them from the experimental ones. Both the experimental and the social stimulus animals had no prior exposure to the test apparatus. Data were collected during 18 2-minute observation periods interpolated over 78 minutes. The 18 periods were grouped into 6 trials (T1,T2,T3,T4,T5,T6) with an interperiod interval of 1 minute and an intertrial interval of 5 minutes. Thus, each trial consisted of 3 2-minute periods. During T1,T3, and T5 (ALONE trials), the experimental animal was alone in the test box, while during T2,T4, and T6 (SOCIAL trials), it was paired with a non-drugged social stimulus animal. Onset of behaviors of the experimental animals was recorded continously during all of the 2-minute periods by using 14 exclusive (and comprehensive) and 1 non-exclusive behavioral categories. The exclusive categories were: Locomote, Sniff, Head-down, Nod, Self-groom, Rear, Gnaw, Rear-gnaw, Jump, Allogroom, Aggress, Submit, Allosniff, and Inactive. The nonexclusive behavior was 90° turns (Table 1). From preliminary studies, these categories describe all the behaviors emitted by the animals. Since the categories were mutually exclusive, onset of one behavior signalled the offset of the previous behavior. Two kinds of reliability measures were taken : test-retest and interjudge. Testing consisted of coding videotaped behaviors of both normal and drugged rats. Two statistics were used for the estimate of reliability : the Kappa coefficient (Cohen, 1960)(Appendix C,Table 1,2), and a multiple correlation on agreement across all behavioral categories coded (Appendix C,Table 3). Test-retest trial yielded a Kappa coefficient of 0.87 while the interjudge trial yielded a Kappa coefficient of 0.76. Both of these coefficients were significant at $p<.001$ (z statistic). On the other hand, the multiple correlation yielded very high aggrements for both test-retest and interjudge trials : 0.998 for normal and 1.000 for the drugged rats on test-retest trials; 0.999 for both normal and drugged rats on interjudge trials. The discrepancy between the two statistical measures was likely due to the fairly

Table 1

DESCRIPTION OF BEHAVIORAL CATEGORIES[1]

Code	Behavior	Description
Q	Locomote	rat moving forward using all four of its legs, crossing lines marked on the test floor; rat usually sniffing as well. The code is activated each time the rat crosses a line with its forelegs in order to record the number of line crosses per bout of locomotion.
G	Sniff	while stationary, rat scans the environment by variable movements of its head; often one can see movements of the whiskers as well.
E	Head-down	while stationary, rat's head is held below the horizontal line of its body with no scanning movements. This posture is often maintained even while rat is locomoting (but only scored while rat is stationary).
X	Nod	while stationary, rat makes repetitive up-and-down movements with its head. This is contrasted with the variable scanning of G and the motionless stance of E.
T	Self-groom	while stationary, rat cleans own face and body with paws, licks its fur or scratches itself with its paws.
W	Rear	while stationary, rat stands on its own hindlegs, usually sniffing as well.
Z	Gnaw	while stationary, rat grinds its teeth against the floor of the test box. The noise made can easily be heard.

C	Rear-gnaw	while rearing, rat grinds its teeth against the side of the test box. The noise made can easily be heard.
L	Jump	rat leaps (all four legs in the air) away from the floor of the test box, often occurring at the corners of the test box.
A	Allogroom	(SOCIAL trials only) rat grooms non-injected rat, usually at the neck region, sometimes at the flank region as well.
S	Aggress	(SOCIAL trials only) rat pins non-injected rat onto the floor of the test box, or rat charges at the other and attepmts to bite at the neck and/or other regions of the other's body.
D	Submit	(SOCIAL trials only) rat crouches motionless while non-injected rat attacks or grooms it, or when rat is being pinned by the non-injected rat.
F	Allosniff	(SOCIAL trials only) rat sniffs the non-injected rat , especially at the anal region.
Y	Inactive	rat motionless, not engaging in any of the above behaviors:usually in a sitting or lying down posture.
R	Turn	rat makes a 90° turn while engaging in any of the above behaviors except Inactive.

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[1] except as indicated, categories were used in all of the trials.

conservative estimate of agreement of the Kappa statistic as well as to the stringent matching criterion used for the tabulation of an agreement -1/60 second- in the test trials.

E. Data Analysis

Raw data from the individual periods were blocked into the six trials prior to data analysis. Data from each behavioral category were then expressed by the following dependent measures: Event Count, Event Probability, Event Rate, Event Duration, Total Bout Duration, and Duration Probability. Event Count was calculated as the total number of non-consecutive occurrences of a particular behavior 'x' in trial 'y'. Event Probability was calculated as the Event Count of behavior 'x' in trial 'y' divided by the total Event Count of all behaviors in 'y'. Event Rate was calculated as Event Count of behavior 'x' divided by the total observation time (in minutes) in trial 'y'. Event Duration (mean) was calculated as the total time (in seconds) engaged in behavior 'x' in trial 'y' divided by the Event Count of 'x' in 'y'. Total Bout Duration was calculated as the total time (in seconds) engaged in behavior 'x' in trial 'y'. Duration Probability was calculated as the Total Bout Duration of behavior 'x' divided by total observation time (in seconds) in trial 'y'. Based on preliminary studies, three dependent measures, Event Count (EC), Event Duration (ED), and Duration

Probability (DP), were chosen as critical measures for this study because of their ability to discriminate differential effects of drugs on the animal's behavior.

In addition, eight new measures were generated by manipulation of the data from the behavioral categories. These are: Total Jump, Composite Social, Composite Stereotypy, Gnaw+Nod, Gnaw+Rear-gnaw, Number of line crosses while locomoting (LC), Number of line crosses per minute of locomotion (Lc/loco), and the Interval (seconds) between consecutive line crosses (ILC). Total Jump was calculated as the total number of jumps - both consecutive and non-consecutive - made by an animal in trial 'y'. Composite Social was calculated by summing across all four social behaviors (Allogroom, Aggress, Submit, Allosniff) within trial (T2,T4,T6) and dependent measure (Event Count, Event Duration, and Duration Probability). Composite Stereotypy (Gnaw+Nod+Rear-gnaw), Gnaw+Nod, and Gnaw+Rear-gnaw were derived post hoc and were dealt with in the Results section. Line crossing was recorded using the same code (Q) as Locomote. Thus, the Number of line crosses was calculated as the total number of consecutive occurrence of 'Q' in trial 'y'. Number of line crosses per minute of locomotion (rate of locomotion) was calculated as the total number of line crosses divided by the Bout Duration of Locomote in trial 'y'. The Interval between consecutive line crosses was calculated as the mean interval from all bouts of Locomote in trial 'y'.

A preliminary analysis of variance was performed separately on each of the three dependent measures for each behavioral category (except for the social behaviors) in order to determine if there was a main effect of ALONE versus SOCIAL conditions (Appendix B,Table 1 to 15). For those dependent measures where there was a significant ($p<.05$) condition effect, group means were calculated by averaging across trials T1,T3, and T5 (for ALONE trial means) and separately across trials T2,T4, and T6 (for SOCIAL trial means). For those measures where there was a nonsignificant condition effect, group means were calculated by averaging across trials T1 to T6 (for TOTAL trial means). Duncan's Multiple Range Test (with alpha level at $p<.05$) was then used to analyze the appropriate means. There was not always a consistent condition effect across all three dependent measures for each of the behavioral category. Those nonconsistent behavioral categories were: Rear, Sniff, Self-groom, Nod, Gnaw+Nod, and Gnaw+Nod+Rear-gnaw. An analysis of variance was also performed on the social behaviors in order to determine any group and trial main effects (Appendix B, Table 16 to 20). Group means for the social behaviors were calculated by averaging across trials T2,T4, and T6 (Appendix A,Table 16). Duncan's Test was also used to analyze these group means. For purpose of reference, group means averaged across ALONE, SOCIAL, and TOTAL trials have been provided separately for each behavioral category and its dependent measures (Appendix A,Table 1 to 15). Data from the non-exclusive behavior - Turn - was processed in a similar manner. The result was that it was not a discriminative category in this study. Thus it was dropped from further consideration.

IV. RESULTS

A. Post Hoc Measures and Behavioral Definitions

Three behavioral effects of Apo were of interest in this study. These were: stereotypy, hyperactivity, and hyperreactivity. Each was defined subsequent to data collection.

Stereotypy. A Composite Stereotypy score was complied by summing across behaviors: Gnaw, Nod, and Rear-gnaw within trial (T1,T2,T3,T4,T5,T6) and dependent measure (Event Count, Event Duration, and Duration Probability). In addition, two behavioral combinations within this group were generated by summing Nod with Gnaw , and Rear-gnaw with Gnaw. The Composite Stereotypy score was derived from a combination of both conceptual and statistical considerations. First, the behaviors: Head-down, Nod, and Rear-gnaw were all significantly different from the saline control group (see section on Apo effects). Although Gnaw was not significantly different from zero in the saline-Apo group, it was included as part of the Composite score because there has been considerable consensus among researchers that gnawing represents an extreme form of Apo-induced stereotypy (Costall & Naylor, 1973; Ernst, 1967; Sahakian et al., 1975). Second, although Head-down was significantly different from zero in the saline-Apo group, it was excluded from the Composite score because it had a different time profile. Time profiles were generated by plotting the Duration Probabilities across the six trials of Head-down, Gnaw, Nod, and Rear-gnaw (Figure 1 to 4). This revealed that while the Duration Probability of Head-down (Figure 1) peaked at the beginning of the test session (T1 significantly different from T3, *t*(9),$p<.02$) and the Duration Probability of Nod (Figure 2) - an intermediate form of stereotypy (see section on Apo effects) - peaked near the end of the test session (T4 significantly different from T5, *t*(9), $p<.05$). The time profiles of Gnaw (Figure 3) and Rear-gnaw (Figure 4) did not have any single significant peak. Thus Head-dwon was excluded because it had a different time profile. Finally, the inclusion of Rear-gnaw in the Composite Stereotypy score was because of its similarity to Gnaw (Table 1).

Hyperactivity. The number of photobeam interruptions over a set period of time has been widely used as an index of activity (Meyerson & Hoglund, 1981). This corresponded closest to the number of line crosses over time in this study. Other related measures were the Number of line crosses per minute of locomotion (rate of locomotion), the Interval between consecutive line crosses, plus Event Count, Event Duration and Duration Probability of Bout Locomotion.

Hyperreactivity. Two measures of hyperreactivity were used in this study: bouts of jumping while alone or in the presence of the non-drugged rat, and the occurrence of more than one jump withing each jumping bout. Jumping is one of the major behaviors assessed in rating scales of reactivity

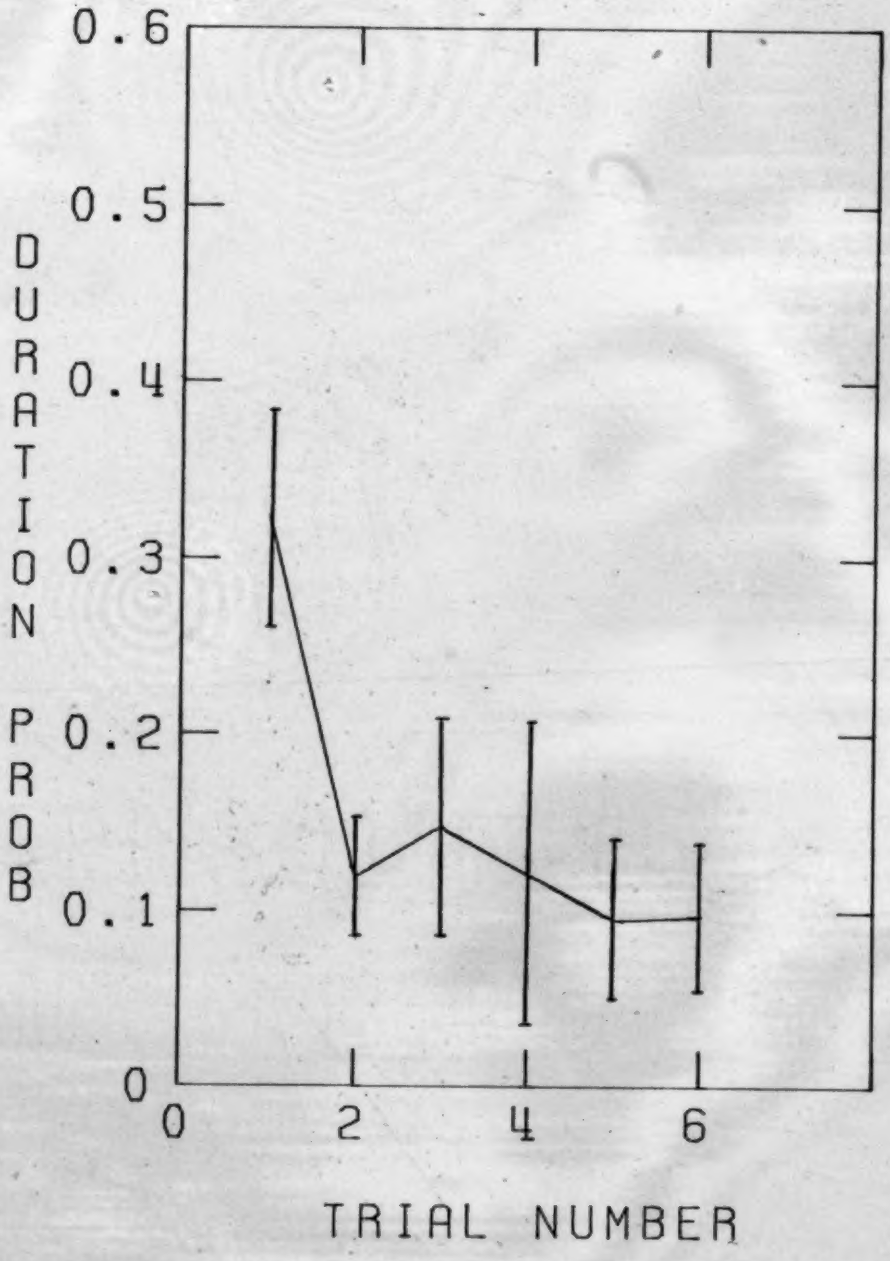

Figure 1

Duration Probability (DP) of Head-down in saline-Apo(5mg/Kg) across the six trials DP of Head-down for saline control is zero (see Table 6, Appendix A)

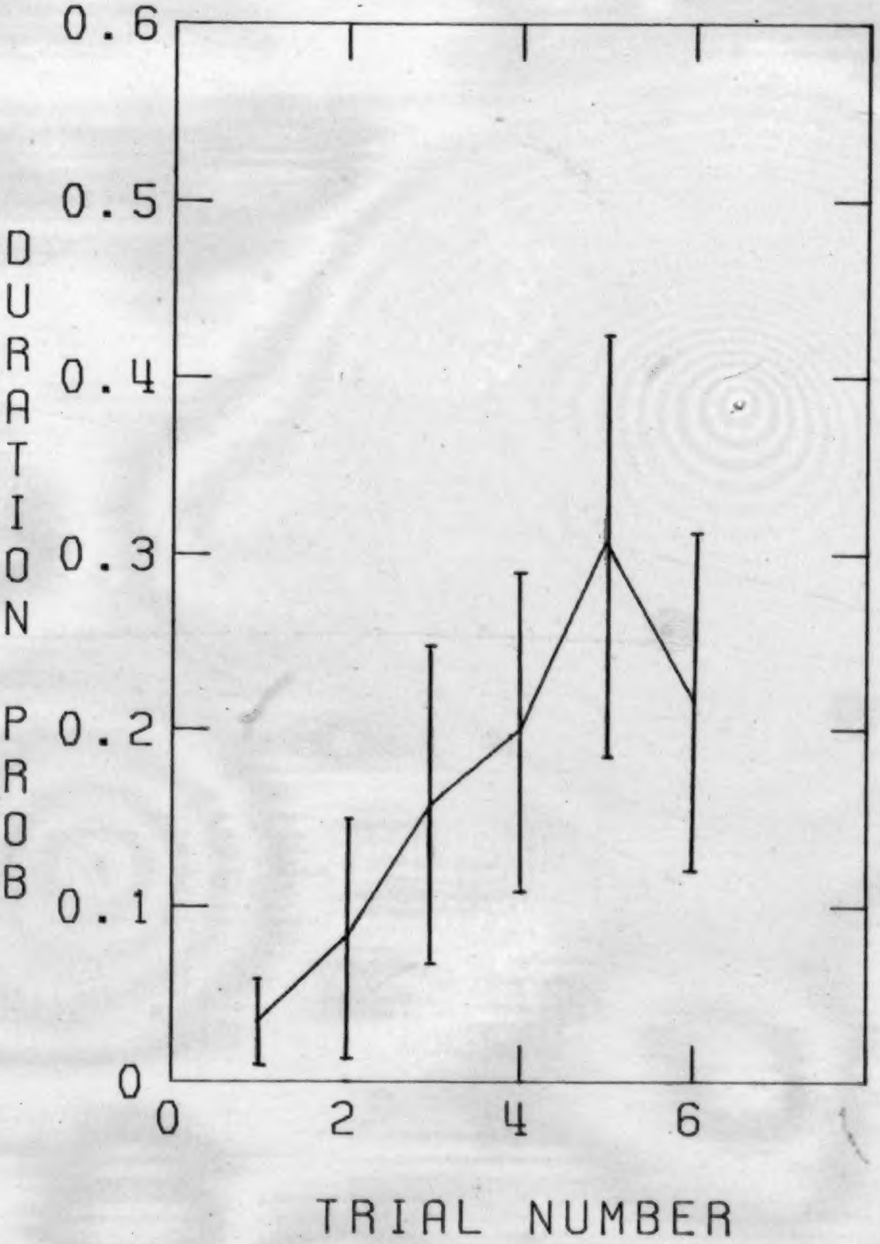

Figure 2

Duration Probability (DP) of Nod in saline-Apo(5mg/Kg) across the six trials DP of Nod for saline control is zero (see Table 7, Appendix A)

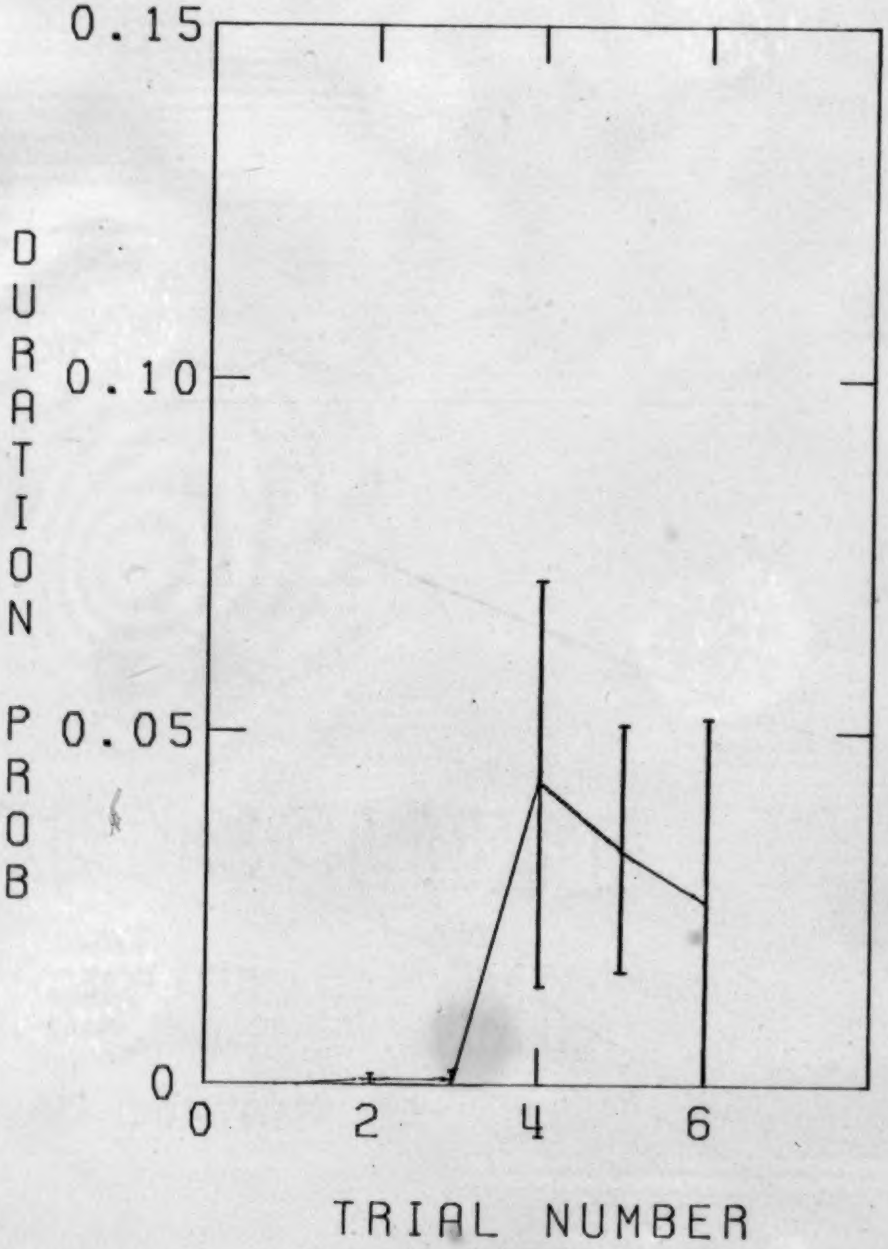

Figure 3

Duration Probability (DP) of Gnaw in saline-Apo(5mg/kg) across the six trials DP of Gnaw for saline control is zero (see Table 8, Appendix A)

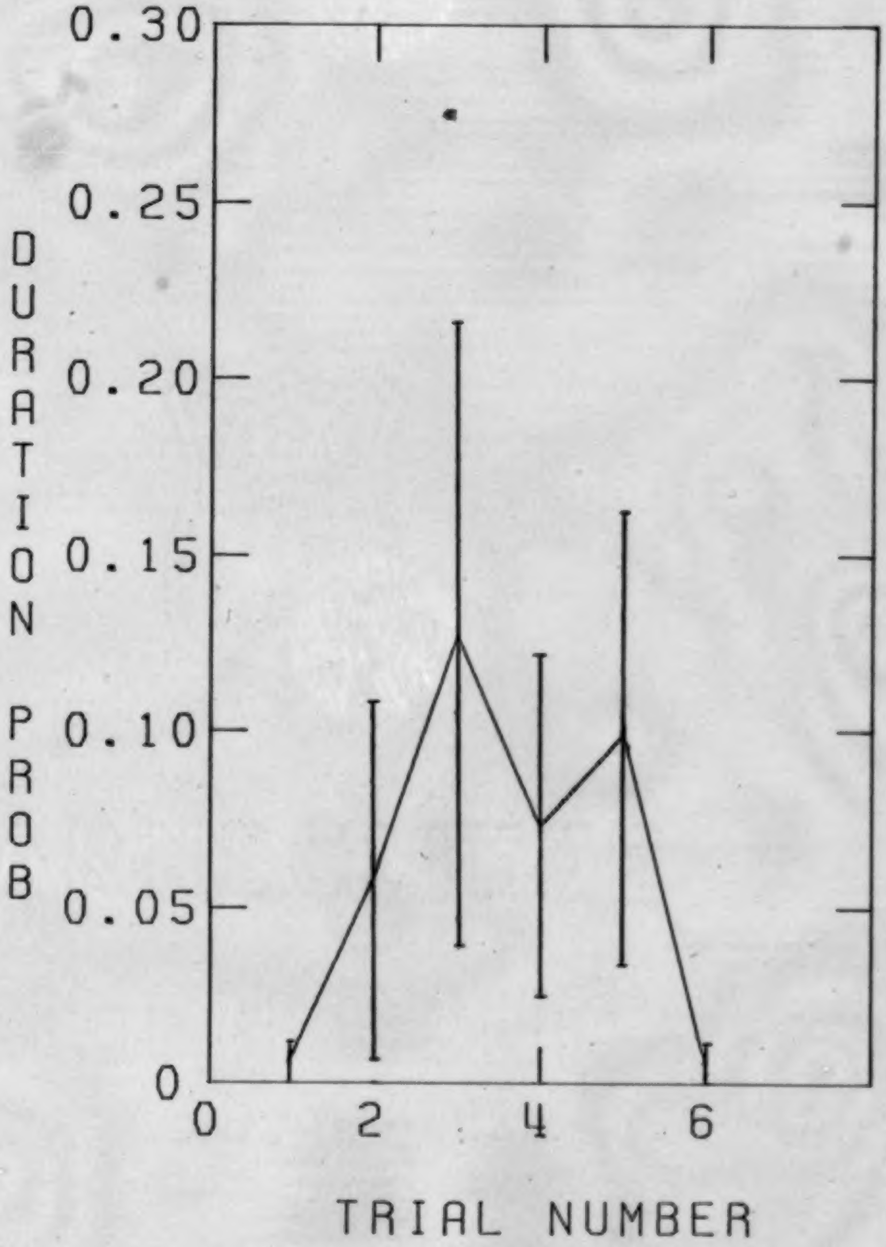

Figure 4

Duration Probability (DP) of Rear-gnaw in saline-Apo(5mg/kg) across the six trials DP of Rear-gnaw for saline control is zero (see Table 9, Appendix A) in septal-lesioned animals (Gage & Olton, 1975). In addition, jumping has been considered a part of the startle response in septal-lesioned animals (Brady & Nauta, 1953). Thus Bout Jump (all three dependent measures) and Total Jump were used to indicate hyperreactivity in this study.

B. Group Main Effect

The detailed analysis of the magnitude and direction of behavior changes of the individual groups contributing to the group main effects will be discussed in sections of the thesis dealing with specific group differences.

For Bout Locomotion (Appendix B,Table 1), there were significant group effects for Event Duration and Duration Probability. These effects were mainly due to the lower level of locomotor activity of the saline control group when compared to all the other drug groups. Likewise, there were significant group effects for the additional measures of hyperactivity: Number of line crosses, Number of line crosses per minute of locomotion, and Interval between consecutive line cross (Appendix B,Table 14). Two factors contribute to the above effects: the relatively low values obtained by the saline control and the relatively high values obtained by the *p*-CA pretreatment groups. Paralleling the effects on activity level, there were significant group effects for all the three dependent measures of Inactive (Appendix B,Table 4). The major contributing factor was the absence of this behavior in all of the drug groups - these animals were continually active.

There were significant group effects for Event Duration and Duration Probability of Sniff (Appendix B,Table 3). The major contributing factor for both effects was the very low levels of sniffing in all of the drug groups when compared to the saline control. There were significant group effects for all of the three dependent measures of Self-groom (Appendix B,Table 5). These effects were due to the very low rate of occurrence of this behavior in all of the drug groups. There were also significant group effects for all of the three dependent measures of Head-down (Appendix B,Table 6). In contrast to Self-groom, these effects were due to the absence of Head-down in the saline control group. Finally, there was no significant group effect for any of the three dependent measures of Rear (Appendix B,Table 2).

There was no significant group effect for any of the three dependent measures of Nod, Gnaw, and Rear-gnaw (Appendix B,Table 7,8,9). This was also the case with the composite stereotypy scores: Gnaw+Nod, Gnaw+Rear-gnaw, and Gnaw+Nod+Rear-gnaw (Appendix B,Table 11,12,13). However, for the hyperreactivity measure Bout Jump, there were significant group effects for all of the three dependent measures (Appendix B,Table 10). This was also the case with Total Jump (Appendix B,Table 15). All these effects on hyperreactivity were due to the high levels of jumping in the *p*-CA pretreatment groups and to the relatively low levels in all the other groups.

For the four social behaviors: Allogroom, Aggress, Submit, and Allosniff as well as the Composite Social, there were significant group effects for all of the three dependent measures (Appendix B, Table 16 to 20). These effects were due to the very low rates of occurrence of social behaviors in all of the drug groups as compared to the saline control.

In summary, the significant group effects in measures of hyperactivity were due to the relatively lower level of locomotor activity of the saline control group. This can be contrasted with the significant group effects of Sniff, where the effects were due to the lower level of sniffing in all the drug groups. The significant group effects of Head-down, Bout Jump and Total Jump were due to the absence of these behaviors in the saline control group. This can be contrasted with the group effects of Inactive, Self-groom, and the social behaviors where these effects were due to the near absence of the particular behaviors in the drug groups. Finally, there were no significant group effects in the dependent measures of Rear plus Gnaw, Nod, Rear-gnaw and their composite scores.

C. Condition Main Effect

As mentioned in the Data Analysis, the result of the test for a condition effect was used to facilitate the appropriate grouping of individual trial means into ALONE, SOCIAL and TOTAL trial means for each behavioral category. A significant condition effect necessitated the trial means to be grouped separately into ALONE (T1,T3, and T5) and SOCIAL (T2,T4, and T6) trial means (Table 2). In the case of a non-significant condition effect, the trials means were grouped into TOTAL (T1 to T6) trial means.

For Bout Locomotion, there were significant facilitative effects over the ALONE condition by the SOCIAl condition for all of the three dependent measures (Appendix B,Table 1). These effects were in the form of increased Event Count, increased Duration Probability and decreased Event Duration during the SOCIAL condition. There were parallel significant effects on the other measures of hyperactivity. There were significantly increased Number of line crosses, Number of line crosses per minute of locomotion, and significantly decreased Interval between consecutive line crosses (Appendix B,Table 14). Finally, the effect of the SOCIAL condition on Inactive was suppression. All the three dependent measures showed significant decreases in the SOCIAL condition when compared to the ALONE condition (Appendix B,Table 4).

Paralleling the effects on activity level, there were significantly more Rear, Sniff, Bout Jump and Total Jump in

Table 2
The Result of Varying Test Condition on Each Behavioral Category[1] and its Dependent Measures

	Measure[2]		
Behavior	EC	ED	DP
Locomote	#	#	#
Rear	#		
Sniff	#	#	
Inactive	#	#	#
Self-groom			#
Head-down	#	#	#
Nod			#
Gnaw			
Rear-gnaw			
Gnaw+Rear-gnaw			
Gnaw+Nod			#
Gnaw+Rear-gnaw+Nod		#	#
Jump	#	#	#

[1] In addition the following measures also had significant Condition effect: Number of line crosses, Number of line crosses per minute of locomotion, Interval between consecutive line crosses, and Total Jump.

[2] EC=Event Count
ED=Event Duration
DP=Duration Probability

significant (p<.05) condition effect (ALONE vs SOCIAL trials)

the SOCIAL condition when compared to the ALONE condition. For Rear, only Event Count showed a significant condition effect (Appendix B,Table 2). For Sniff, there were significant condition effects for Event Count and Event Duration (Appendix B,Table 3). Event Count of Sniff was significantly increased during the SOCIAL condition while the Event Duration was significantly decreased during the SOCIAL condition. For Bout Jump, all of the three dependent measures were significantly increased during the SOCIAL condition (Appendix B,Table 10). This was also the case for Total Jump (Appendix B,Table 15).

In contrast to the facilitation on activity level, there were significantly less Self-groom, Head-down, and stereotypic behaviors during the SOCIAL condition. For Self-groom, only Duration Probability had a significant condition effect (Appendix B,Table 5). For Head-down, all of the three dependent measures were significantly decreased during the SOCIAL condition (Appendix B,Table 6). For Nod as well as for Gnaw+Nod, only Duration Probability had a significant condition effect (Appendix B,Table 7,11). However, for the Composite Stereotypy Score (Gnaw+Nod+Rear-gnaw), there were significant effects for both Event Duration and Duration Probability (Appendix B,Table 13).

In summary, the presence of the non-drugged rat facilitated measures of locomotor activity, of reactivity (Jump), and of explorative behaviors (Rear, Sniff). There were suppressive effects on Self-groom, Inactive, Head-down, and measures of stereotypy.

D. Group X Condition Interaction

There were only a few significant group x condition interactions. These were primarily due to the differential reactions of the saline control group to the ALONE and SOCIAL conditions as compared to all the drug groups. For Bout Locomotion, there were significant interactions for all three dependent measures (Appendix B,Table 1). Overall, the saline group showed greater social facilitative effect (in all three measures) than all the other drug groups. The absolute level of locomotor activity was however lower for the saline group than all others in the ALONE condition (Appendix A,Table 1). There were also significant interactions in the other measures of hyperactivity: Number of line crosses, Number of line crosses per minute of locomotion, and Interval between consecutive line crosses (Appendix B,Table 14). The factors contributing to these interactions were the same as those for the dependent measures of Bout Locomotion (Appendix A,Table 14).

For Sniff, both Event Duration and Duration Probability showed significant interactions (Appendix B,Table 3). While these two measures of the saline group decreased during the SOCIAL condition, those of the drug groups increased (Appendix A,Table 3). As well, the values of both Event

Duration and Duration Probability were higher for the saline group than the drug groups in the ALONE condition (Appendix A,Table 3).

For Inactive, all three dependent measures showed significant interactions (Appendix B,Table 4). These interactions were due to the absence of Inactive in the drug groups as well as to a strong suppression of Inactive in the saline group during the SOCIAL condition (Appendix A,Table 4). There were also significant interactions for Event Duration and Duration Probability of Self-groom (Appendix B,Table 5). The factors contributing to these interactions were the same as those for Inactive (Appendix A,Table 5). Finally, there was a significant interaction for Duration Probability of Head-down (Appendix B,Table 6). This interaction was due to the absence of this behavior in the saline group as well as to a moderate suppression of Head-down in the drug groups during the SOCIAL condition (Appendix A,Table 6).

In summary, the significant interactions were primarily due to the differential reations of the saline group to the ALONE and SOCIAL conditions. Thus, the saline group had a lower level of locomotor activity in the ALONE condition, and an absence of Head-down in both conditions. In contrast, the drug groups had lower values for Sniff in the ALONE condition and an absence of Inactive as well as Self-groom in both ALONE and SOCIAL conditions.

E. Apo Behavioral Effects

(group 2 versus group 1)

Duncan's Multiple Ranges Test (with alpha at 0.5) was used to compare the saline-Apo (group 2) with the saline control (group 1) (Table 3,4).

t-tests comparing ALONE with SOCIAL trials within a group for a particular dependent measure were also used to determine the specific effects of varying condition on the different behaviors.

The saline-Apo group was significantly more hyperactive than its saline control in the ALONE condition (Appendix A,Table 1,14). This was reflected in significant increases in Event Count, Event Duration and Duration Probability of Bout Locomotion, plus the Number of line crosses during locomotion. The Number of line crosses per minute of locomotion was greater and the Interval between consecutive line crosses smaller but these changes were not significant.

Table 3
Results of Duncan's Multiple Ranges Test of the Six Groups on Behaviors of the Normal Rat in ALONE, SOCIAL or TOTAL trials

	Behaviors												
Comparisons[1]	Locomote		Rear			Sniff			Inactive		Self-groom		
	A	S	A	S	T	A	S	T	A	S	A	S	T
S/APO VS S/S	C[2]+ D+ P+	D+				D#	C#	P#	C# D# P#		P#	P#	C# D#
p-CPA(400) VS S/APO													
p-CA(10.4) vs S/APO													
p-CPA(400) vs p-CA(10.4)	D+	D+											
p-CPA(250) vs S/APO													
p-CA(6.4) vs S/APO													
p-CPA(250) vs P-CA(6.4)													

[1] S/Apo =group 2
S/S =group 1
p-CPA(400)=group 3
p-CA(10.4)=group 5
p-CPA(250)=group 4
p-CA(6.4) =group 6

[2] C=Event Count
D=Event Duration
P=Duration Probability

+ indicates first group in the comparison is significantly greater than (p<.05) the second group
# indicates first group in the comparison is significantly less than (p<.05) the second group

Table 4
Results of Duncan's Multiple Ranges Test of the Six Groups on the Additional Measures in ALONE or SOCIAL trials

	Behaviors[1]							
	LC		LC/loco		ILC		TOTAL JUMP	
Comparisons[2]	A	S	A	S	A	S	A	S
S/APO VS S/S	+					#		
p-CPA(400) VS S/APO								
p-CA(10.4) vs S/APO	+		+		#			
p-CPA(400) vs p-CA(10.4)	#	#		#	+	+		
p-CPA(250) vs S/APO								
p-CA(6.4) vs S/APO	+		+		#		+	+
p-CPA(250) vs P-CA(6.4)							#	

[1] LC=Number of line crosses during locomotion
Lc/loco=Number of line crosses per minute of locomotion
ILC=Interval between consecutive line crosses

[2] S/APO =group2
S/S =group1
p-CPA(400)=group3
p-CA(10.4)=group5
p-CPA(250)=group4
p-CA(6.4) =group6

+ indicates first group in the comparison is significantly greater than ($p<.05$) the second group
# indicates first group in the comparison is significantly less than ($p<.05$) the second group

This was contrasted in the SOCIAL condition, where only the Event Duration of Bout Locomotion (increased) and the Interval between consecutive line crosses (decreased) were significantly different from the saline control. Although both groups showed a significant facilitation of locomotor activity in the SOCIAL condition as compared to the ALONE condition, the facilitation was greater for the saline control group (EC:$t(9)=9.24, p<.0005$ and DP:$t(9)=9.53, p<.0005$ for saline control. EC:$t(9)=3.44$, $p<.007$ and DP:$t(9)=2.57, p<.03$ for saline-Apo)

Parallelling the increased locomotor activity in the ALONE condition, the saline-Apo group was significantly less inactive than its saline control. Thus while the saline control group spent approximately 1/4 (.23±.04) of the time inactive, the saline-Apo group was continually active (Appendix A,Table 4). This difference was reflected in significant decreases in Event Count, Event Duration, and Duration Probability (all for ALONE trials) of Inactive for the saline-Apo group. However, this difference disappeared during the SOCIAL condition as the saline control group also became continually active.

The saline-Apo group sniffed (Sniff) and groomed (Self-groom) significantly less than its saline control in both ALONE and SOCIAL conditions (Appendix A,Table 3,5). For sniffing, this was reflected in significant decreases in Event Duration (ALONE trials only), Event Count (SOCIAL trials only) and Duration Probability (TOTAL trials). For self-grooming, this was reflected in significant decreases in Duration Probability (both ALONE and SOCIAL trials), Event Count (TOTAL trials) and Event Duration (TOTAL trials). Furthermore, while for the saline control group, both sniffing and self-grooming decreased in the presence of the non-drugged rat, there was no similar effect for the saline-Apo group (EC:$t(9)=4.14, p<.003$, ED:$t(9)=5.65, p<.001$, and DP:$t(9)=3.79$, $p<.004$ for Sniff- saline control; ED:$t(9)=3.18, p<.005$ and DP:$t(9)=2.30, p<.047$ for Self-groom saline control) The saline-Apo group also showed a two-fold decrease in Event Count (both ALONE and SOCIAL trials) coupled with a two-fold increase in Event Duration (TOTAL trials) of Rear when compared to its saline control (Appendix A,Table 2). However, these changes were not significant.

The saline-Apo group also showed significantly less social interaction with the non-drugged rat in the SOCIAL trials than its saline control (Appendix A,Table 16 to 20). This was reflected in significant decrease in Event Count, Event Duration and Duration Probability for all the four social behaviors: Allogroom, Aggress, Submit, Allosniff, as well as for the Composite Social Category.

In addition to changes in existing behaviors exhibited by the saline control group, Apo generated the following new behaviors: Head-down, Nod, Gnaw, Rear-gnaw, and Jump (Table 5). Although the saline control group did not exhibit any of these behaviors, Gnaw and Jump were not significantly

Table 5
Results of Duncan's Multiple Ranges Test of the Six Groups on Apo-induced Behaviors in ALONE, SOCIAL or TOTAL trials

	Behaviors											
	Head-down		Nod			Gnaw	Rear-Gnaw	Composite[2]			Jump	
Comparisons[1]	A	S	A	S	T	T	T	A	S	T	A	S
S/APO VS S/S	C[3]+ D+ P+	C D+ P+	P+	P+	D+		D+ P+	P+	C+			
p-CPA(400) VS S/APO				P#	D#	D+ P+	D# P#					
p-CA(10.4) vs S/APO				P#	D#		D# P#					D+
p-CPA(400) vs p-CA(10.4)						D+ P+						
p-CPA(250) vs S/APO							D# P#					
p-CA(6.4) vs S/APO							D# P#				C+ D+ P+	C+ D+ P+
p-CPA(250) vs P-CA(6.4)											C+ D+ P+	

[1] S/Apo =group 2
S/S =group 1
p-CPA(400)=group 3
p-CA(10.4)=group 5
p-CPA(250)=group 4
p-CA(6.4) =group 6

[2] Composite=Gnaw+Nod+Gnaw
The other two subsets:Gnaw+Nod, and Gnaw+rear-gnaw did not have any significant comparisons.

[3] C=Event Count
D=Event Duration
P=Duration Probability

+ indicates first group in the comparison is significantly greater than ($p<.05$) the second group

# indicates first group in the comparison is significantly less than ($p<.05$) the second group different from zero. For Head-down, the increases in Event Count, Event Duration, and Duration Probability (both ALONE and SOCIAL trials) were significantly different from zero (Appendix A,Table 6). For Nod, the increases in Duration Probability (both ALONE and SOCIAL trials) and Event Duration(TOTAL trials) were significantly different from zero (Appendix A,TAble 7). For Rear-gnaw, the increases in Duration Probability and Event Duration (both for TOTAL trials) were significantly different from zero (Appendix A,Table 9). For the Composite Stereotypy Score, the increases in Event Count (TOTAL trials) and Duration Probability (both ALONE and SOCIAL trials) were also significantly different from zero (Appendix A,Table 13). However, neither of the two subsets (Gnaw+Nod, Gnaw+Rear-gnaw) was significantly different from zero.

The behavioral effects of Apo could be viewed in a different perspective by presenting the three major components : hyperactivity, hyperreactivity, and stereotypy in a trial-by-dependent variable format (Figure 5,6,7). This perspective attempted to investigate the interrelationships among the three behavioral components of the Apo effect and the effects of a changing environment (ALONE versus SOCIAL) on these components.

Each of the three components had its own characteristic profile. Hyperactivity, expressed as the Number of line

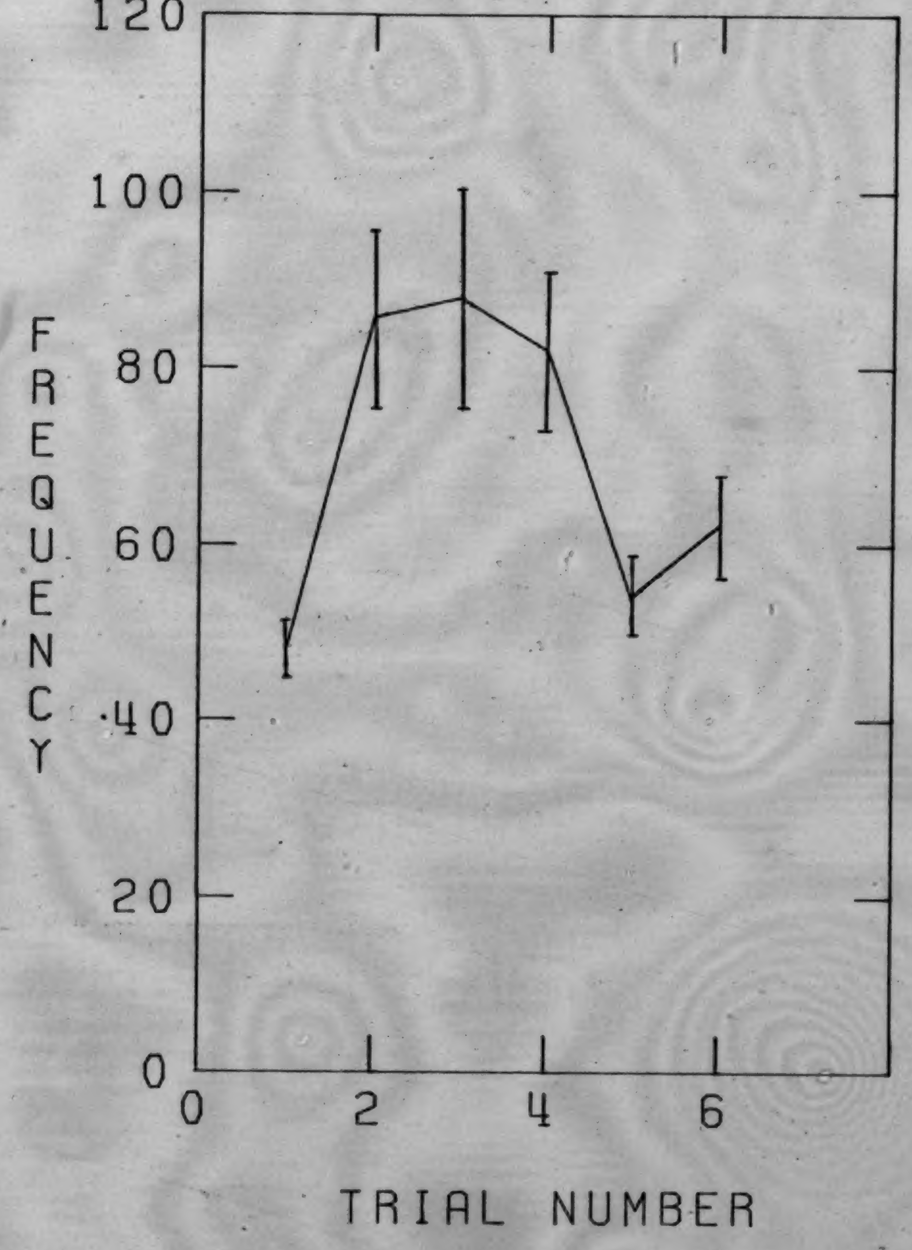

Figure 5

Frequency of Line Cross per minute of Locomote in saline-Apo(5mg/kg) across the six trials

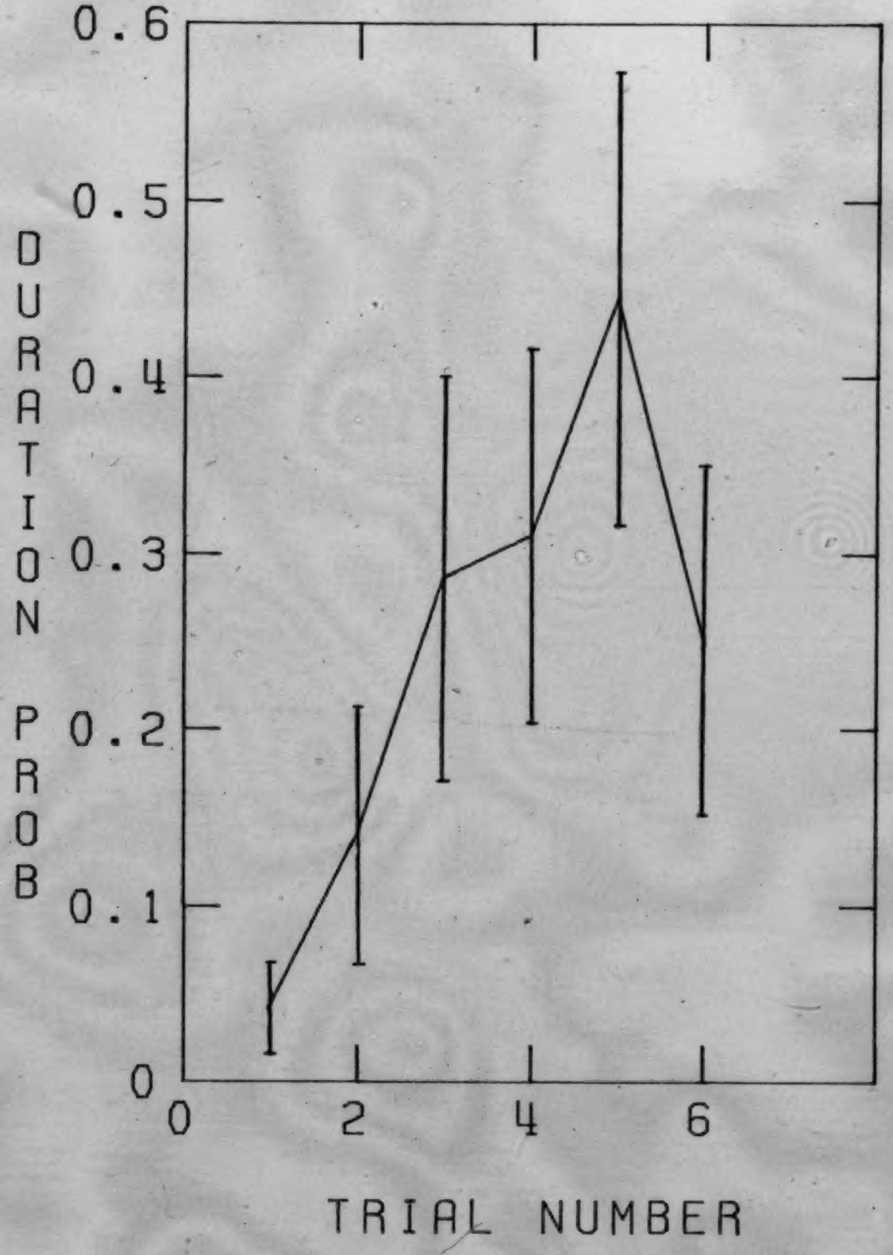

Figure 6

Duration Probability (DP) of the Composite Stereotypy Score (Gnaw+Nod+Rear-gnaw) in the saline-Apo(5mg/kg) across the six trials DP of this behavior for saline control is zero (see Table 13, Appendix A)

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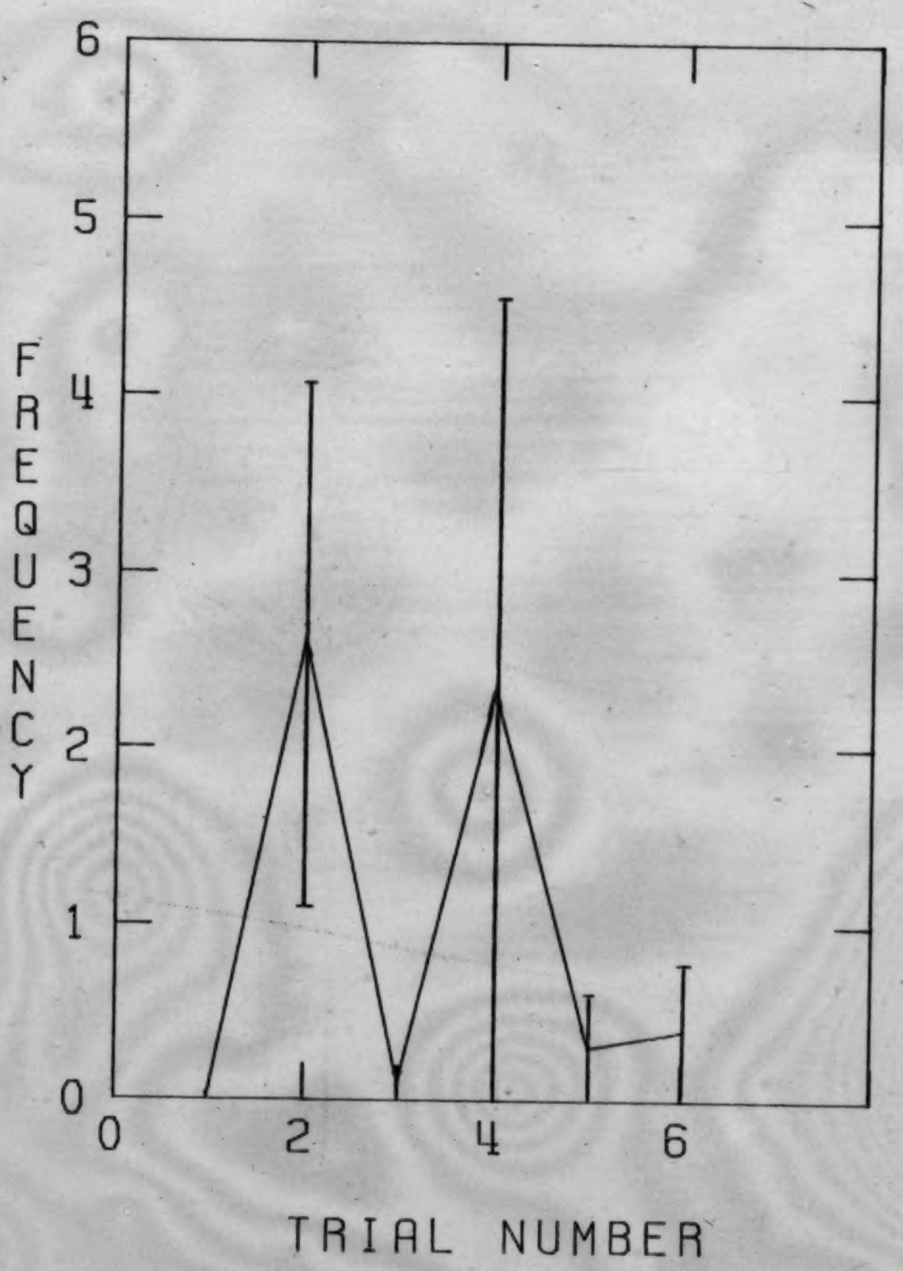

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Figure 7

Frequency of Total Jump in saline-Apo(5mg/kg) across the six trials
Frequency of Total Jump for the saline control is zero (see Table 15, Appendix A)

crosses per minute of locomotion (rate of locomotion), had a relatively symmetrical time profile that plateaued during trials 2,3,and 4 (Figure 5) (T1 significantly different from T2, $t(9)=4.10, p<.003$; T4 different from T5, $t(9)=4.54$, $p<.001$). It was relatively unaffected by the presence of the non-drugged rat (T2 not different from T3, $t(9)=0.34, p<.7$). This profile could be contrasted to that of the saline control (Figure 8), where the same measure varied greatly as a function of the presence of the non-drugged rat (all adjacent trials were significantly different from each other, *t*-tests). Stereotypy, expressed as the Duration Probability of the Composite Stereotypy Score, had a more skewed time profile that peaked in Trial 5 (Figure 6) (T4 different from T5, $t(9)=2.65, p<.027$; T5 different from T6, $t(9)=2.80, p<.021$). Like the hyperactivity measure, it also was relatively unaffected by the presence of the non-drugged rat. On the other hand, hyperreactivity, expressed as the frequency of Total Jump, had a time profile that showed a tendency towards reactivity to the non-drugged rat - peaking in Trials 2 and 4 (Figure 7). However, the increases in trials 2 and 4 were not significantly different from the rest of the trials (*t*-tests). Finally, the level of stereotypy was still relatively high at Trial 6 (the end of the test session) whereas both hyperactivity and

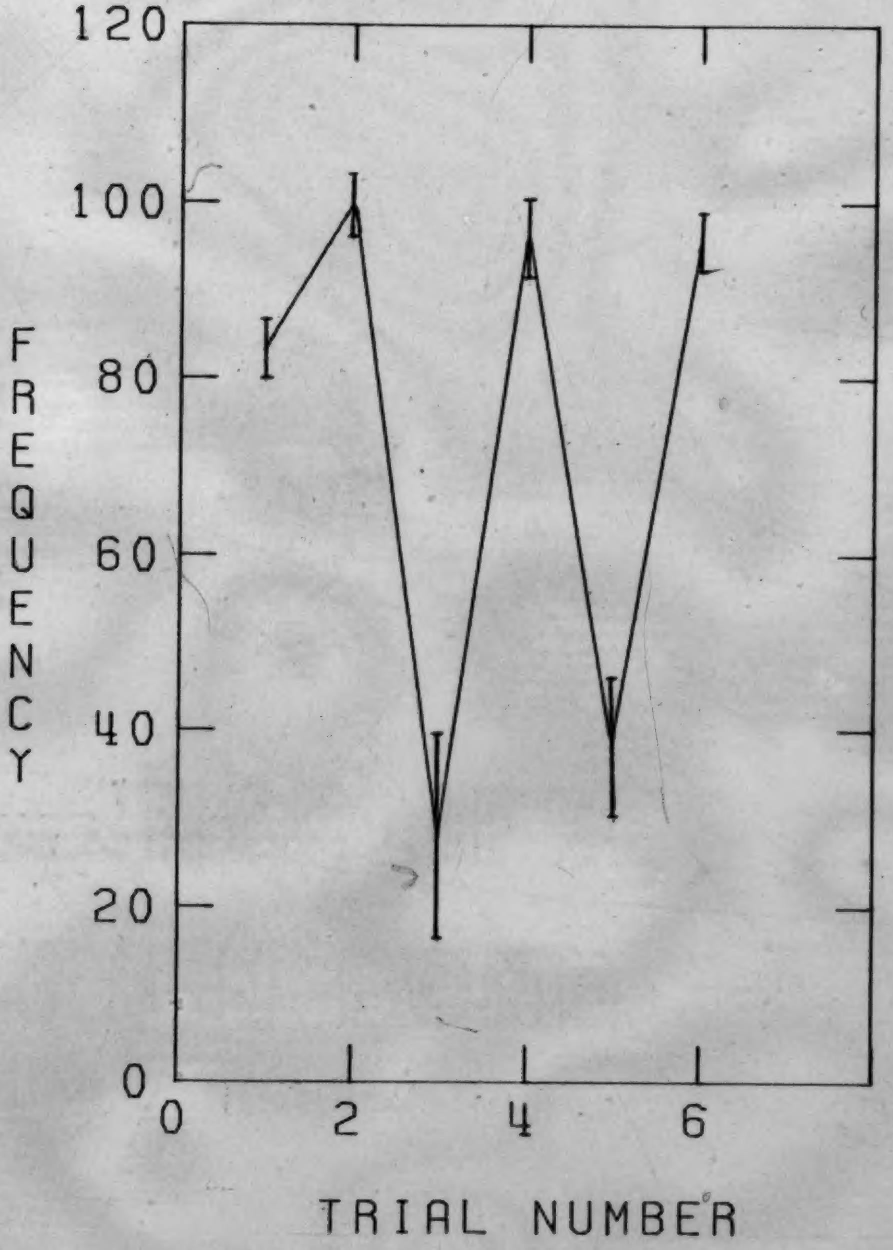

Figure 8

Frequency of Line Crosses per minute of
Locomote in saline control across the six trials

hyperreactivity effects were already dissipating (See Figure 6 with Figure 5, 7). Thus, in summary, the Apo-induced hyperactivity, stereotypy and hyperreactivity each had its own characterestic time profile. Although each showed maximal activity at different times during the observation session, there was no clear order-of-appearance effect. Finally, the presence of the non-drugged rat had differential effects on the three components.

In summary, administration of Apo to a normal animal significantly modified existing behaviors : increased locomotor activity, decreased sniffing, self-grooming, inactivity and social interactions. These modifications were consistent for all the three dependent measures of each of the behaviors. In addition, whereas the effects of the presence of the non-drugged rat for the saline control group were increased locomotor activity, decreased inactivity, self-grooming and sniffing, the effect for the saline-Apo group was only an increase in locomotor activity. Finally, Apo also introduced new behaviors : Head-down, Nod, Gnaw, Rear-gnaw and Jump. All of these behaviors were significant except Gnaw and Jump. The increases for Head-down were significant for all the three dependent measures while only Event Duration and Duration Probability were significant measures for Nod and Rear-gnaw.

F. p-CPA Effects on Apo-Induced Behaviors

(groups 3,4 versus group 2)

All *t*-test results cited below refer to ALONE versus SOCIAL trials, paired comparisons within a particular group and dependent measure.

Neither dosages of *p*-CPA had any significant effect on the specific measures of Apo-induced hyperactivity (Figure 9A). Nevertheless, *p*-CPA pretreatment did modify aspects of the hyperactivity. Whereas the presence of the non-drugged rat greatly facilitated the rate of locomotion for the saline-Apo group ($t(9)=4.70, p<.001$ for Number of line crosses per minute of locomotion), this effect was nullified by the *p*-CPA pretreatment ($t(9)=0.32, p<.8$ for the high dose; $t(9)=1.45, p<.18$ for the low dose) Furthermore, pretreatment with high dose *p*-CPA (400mg/kg) actually reversed the effect : the rate of locomotion tended to be slower in the SOCIAL trials than in the ALONE trials (although this difference was not significant).

Similarily, neither dosage of *p*-CPA had a significant effect on the specific measures of hyperreactivity (Figure 10A). However, there was a tendency for potentiation. Pretreatment with either dose of *p*-CPA tended to increase the frequency of both Bout Jump and Total Jump when compared to the saline-Apo group. Furthermore, while the low dose of *p*-CPA (250mg/kg) showed the highest frequency of jumping of

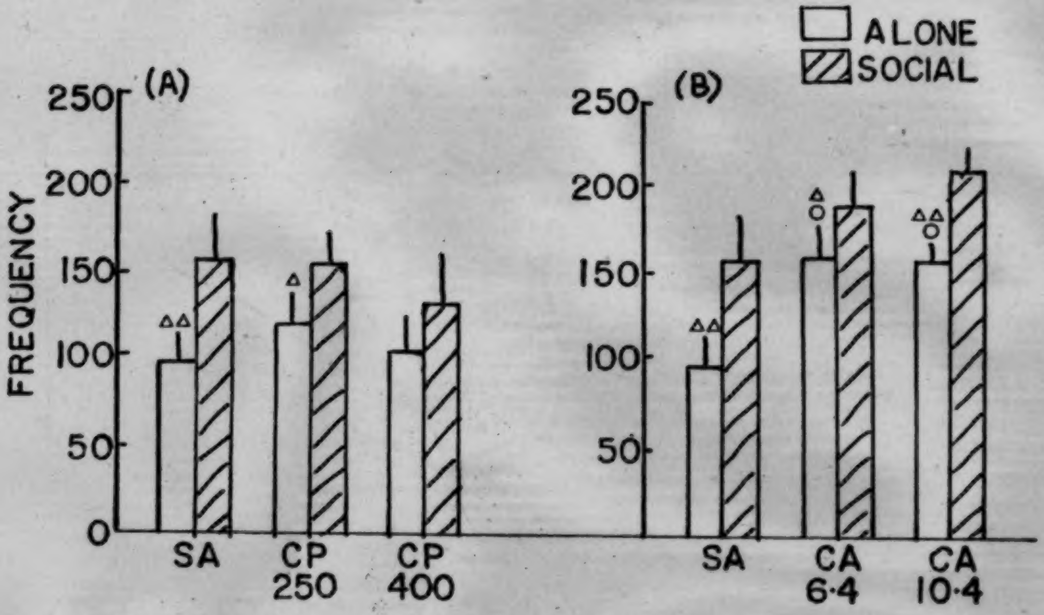

Figure 9

Dose effects of p-CPA (Fig. 9A) and p-CA (Fig. 9B) on Frequency of line cross during ALONE and SOCIAL conditions.

SA =saline-Apo(5mg/kg)
CP250 =p-CPA(250mg/kg)/Apo(5mg/kg)
CP400 =p-CPA(400mg/kg)/Apo(5mg/kg)
CA6.4 =p-CA(6.4mg/kg)/Apo(5mg/kg)
CA10.4 =p-CA(10.4mg/kg)/Apo(5mg/kg)

○ $p<.05$ vs SA (within condition comparison)
△ $p<.05$ vs SOCIAL (within group comparison)
△△ $p<.01$ vs SOCIAL (within group comparison)

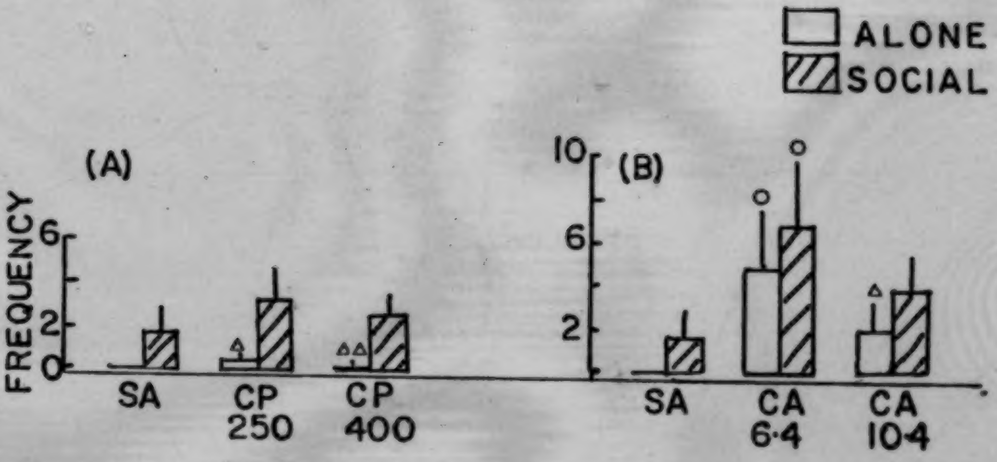

Figure 10

Dose effects of p-CPA (Fig. 10A) and p-CA (Fig. 10B) on Frequency of jumping bouts during ALONE and SOCIAL conditions.
Groups and levels of significance as in Fig. 9

the three groups, the high dose of *p*-CPA (400mg/kg) showed the most reactivity to the presence of the non-drugged rat of the three groups ($t(9)=3.26$, $p<.01$ for *p*-CPA-400mg/kg; $t(9)=2.26$, $p<.05$ for *p*-CPA-250mg/kg; $t(9)=1.38$, $p<.2$ for saline-Apo).

p-CPA pretreatment did have significant effects on specific Apo-induced stereotypic behaviors. Pretreatment with *p*-CPA (400mg/kg) significantly decreased the Event Duration (TOTAL trials) and Duration Probability (SOCIAL trials) of Nod (Figure 11A). This dose of *p*-CPA also significantly decreased the Event Duration (TOTAL trials) and Duration Probability (SOCIAL trials) of Rear-gnaw (Figure 12C). Although the low dose of *p*-CPA (250mg/kg) also affected Nod and Rear-gnaw in a similar way (as the high dose), only the effects on Rear-gnaw were significant (Table 4). While both Nod and Rear-gnaw were decreased by *p*-CPA pretreatment, Gnaw was significantly increased by *p*-CPA pretreament (Figure 12A). Both Event Duration and Duration Probability (both for TOTAL trials) of Gnaw were significantly increased by pretreatment with *p*-CPA (400mg/kg). Although the low dose *p*-CPA (250mg/kg) also affected Gnaw in a similar way (as the high dose), this effect was not significant. Finally, the overall Composite Stereotypy Score was not significantly affected by either *p*-CPA pretreatment.

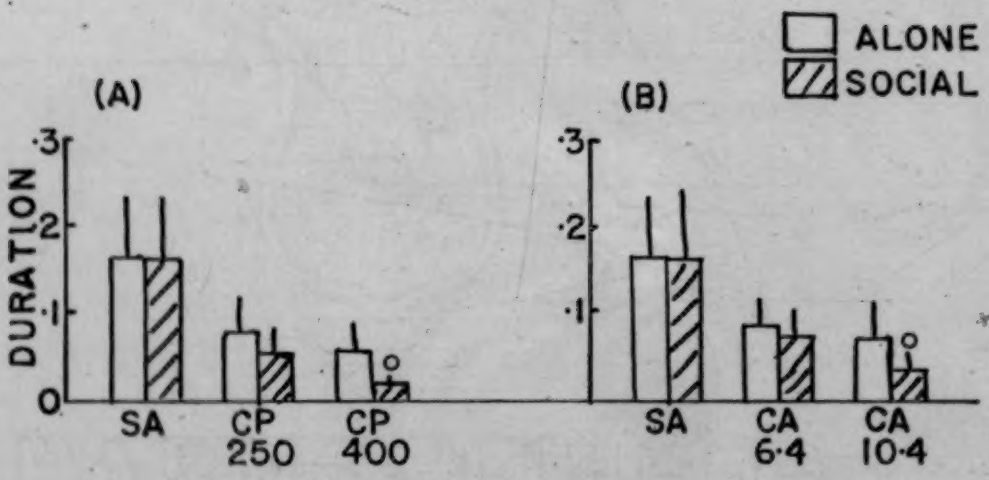

Figure 11

Dose effects of p-CPA (Fig. 11A) and p-CA (Fig. 11B) on Duration Probability of Nod during ALONE and SOCIAL conditions.
Groups and levels of significance as in Fig. 9

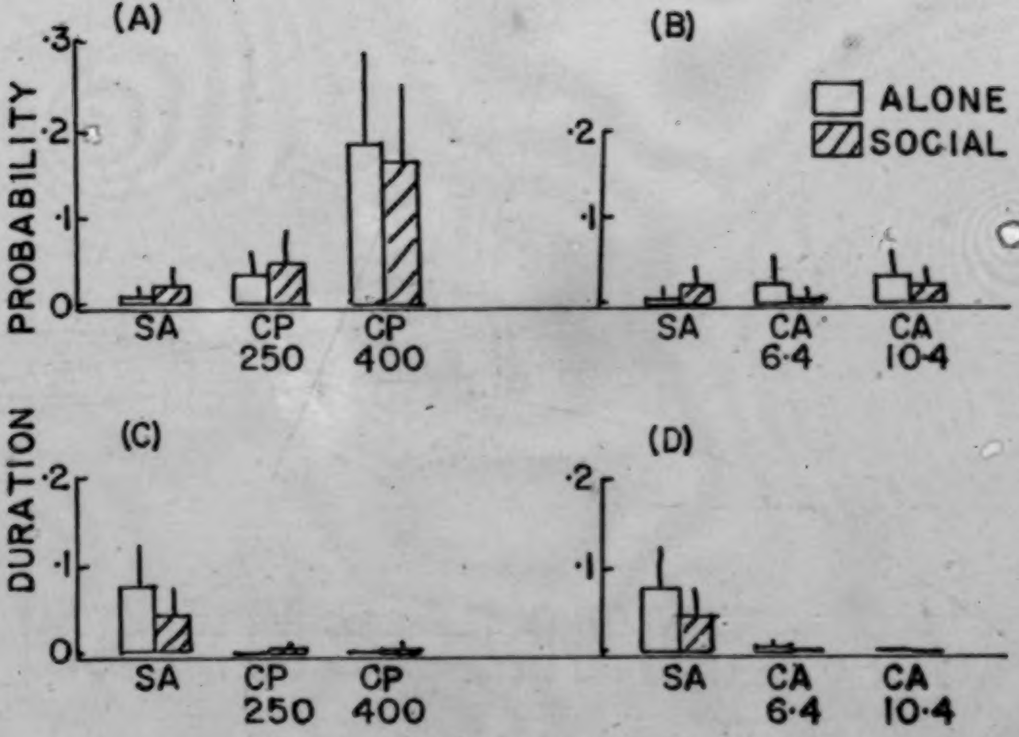

Figure 12

Duration Probability of Gnaw showing dose effects of p-CPA((Fig. 12A) and p-CA (Fig. 12B) plus Duration Probability of Rear-gnaw showing dose effects of p-CPA (Fig. 12C) and p-CA (Fig. 12D). Groups and levels of significance as in Fig. 9

In summary, pretreatment with *p*-CPA altered minor aspects of both Apo-induced hyperactivity and hyperreactivity. The facilitation of locomotion (by the presence of the non-drugged rat) in the saline-Apo group was nullified by *p*-CPA pretreatment (both doses). On the other hand, the facilitation of jumping (by the presence of the non-drugged rat) was potentiated by *p*-CPA (high dose only). The strongest effect of *p*-CPA pretreatment was on the specific stereotypic behaviors (only Event Duration and Duration Probability). Although there was no change in the Composite Stereotypy Score, both Nod and Rear-gnaw were significantly decreased by *p*-CPA pretreatment (especially with the high dose). Gnaw, on the other hand, was significantly increased by pretreatment (high dose only). Finally, pretreatment of *p*-CPA did not alter significantly alter any other aspect of the Apo behavioral effect.

G. p-CA Effects on Apo-Induced Behaviors

(groups 5,6 versus group 2)

t-test results cited below refer to ALONE versus SOCIAL trials, paired comparisons within a group for a particular behavior and dependent measure.

The effect of pretreatment with *p*-CA on Apo-induced hyperactivity was potentiation (Figure 9B). This was reflected in significant increases (ALONE trials only) in several measures of hyperactivity: Number of line crosses, Number of line crosses per minute of locomotion, and the Interval between consecutive line crosses. These increases were significant for both doses of *p*-CA used (Table 4). Like the *p*-CPA pretreatment, the facilitation of the rate of locomotion by the presence of the non-drugged rat was nullified by *p*-CA pretreatment ($t(9)=1.08, p<.31$ for high dose; $t(9)=0.99, p<.35$ for low dose) Both doses showed a decrease in rate during the SOCIAL trials (although the ALONE-SOCIAL difference was not significant).

Like hyperactivity, the effect of pretreatment with *p*-CA on Apo-induced hyperreactivity was also potentiation (Figure 10B). This potentiation was reflected in two ways. One, pretreatment with the low dose (6.4mg/kg) significantly increased both Bout Jump (all three dependent measures, both ALONE and SOCIAL trials) and Total Jump (Event Count, both ALONE and SOCIAL trials). Two, pretreatment with the high dose (10.4mg/kg), while not significantly increasing the absolute level of jumping, did significantly potentiate the facilitation of jumping by the presence of the non-drugged rat ($t(9)=2.57, p<.03$).

The effect of pretreatment with *p*-CA on Apo-induced stereotypy, unlike those on hyperactivity and hyperreactivity, was one of suppression (Table 5). Pretreatment with *p*-CA (10.4mg/kg) significantly decreased both Event Duration (TOTAL trials) and Duration Probability(SOCIAL trials only) of Nod (Figure 11B). Similarily, this same dose of *p*-CA also significantly decreased both Event Duration and Duration Probability (both for TOTAL trials) of Rear-gnaw (Figure 12D). The low dose of *p*-CA (6.4mg/kg) had simliar effects on Nod and Rear-gnaw (as the high dose) but these effects were not significant. Unlike the pretreatment with *p*-CPA, there was no effect on Gnaw by *p*-CA pretreatments. Finally, although pretreatment with *p*-CA (both doses) decreased the Duration Probability and Event Duration of the Composite Stereotypy Score, these effects were not significant.

In summary, pretreatment with *p*-CA significantly modified all three major components of Apo-induced behavior. Several measures of hyperactivity were significantly potentiated by *p*-CA pretreatment, while the facilitation of the rate of locomotion (by the presence of the non-drugged rat) was nullified. Both measures of hyperreactivity - Bout Jump (all three dependent measures) and Total Jump - were significantly potentiated by *p*-CA (low dose only). As well, the facilitation of jumping (by the presence of the non-drugged rat) was also potentiated by *p*-CA (high dose only). Finally, while both pretreatments did not significantly alter the Composite Stereotypy Score, the high dose (10.4mg/kg) did significantly suppress both Nod and Rear-gnaw.

H. Comparison of p-CPA and p-CA Effects on Apo-Induced Behaviors

Duncan's Test (with alpha at 0.5) was used to compare *p*-CPA pretreatments with *p*-CA pretreatments.

Pretreatment with either *p*-CPA or *p*-CA caused significant suppression of Nod and Rear-gnaw (Figure 11A,11B,12C,12D). Both also suppressed the facilitation of the rate of locomotion by the presence of the non-drugged rat. As well, both pretreatments potentiated the facilitation of jumping by the presence of the non-drugged rat. However, there were three specific differences between the effects of these two pretreatments. One, *p*-CPA pretreatment (400mg/kg) resulted in a significant increase of Event Duration and Duration Probability (both for TOTAL trials) of Gnaw when compared to either dose of *p*-CA (10.4mg/kg or 6.4mg/kg) pretreatments (Table 5). Two, the *p*-CA pretreatment (10.4mg/kg) group was significantly more hyperactive than the *p*-CPA pretreatment (400mg/kg) group (Table 5). This was reflected in significant increases in the Number of line crosses (both ALONE and SOCIAL trials), the Number of line crosses per minute of locomotion (SOCIAL trials only), and a concomitant decrease in the Interval between consecutive line crosses (ALONE and SOCIAL trials)(Appendix A,Table 14). In addition, the Event Duration (ALONE and SOCIAL trials) of Bout Locomotion of the *p*-CA (10.4mg/kg) group was significantly shorter than that of the *p*-CPA (400mg/kg) group (Appendix A, Table 1). Three, *p*-CA pretreatment (6.4mg/kg) significantly increased the Bout Jump (all three dependent measures, ALONE trials only) as well as Total Jump (Event Count; ALONE trials only) when compared to *p*-CPA (250mg/kg) pretreatment (Appendix A,Table 10,15).

In summary, pretreatment with high doses of *p*-CPA (400mg/kg) or *p*-CA (10.4mg/kg) altered different aspects of the Apo behavioral effect. Thus, pretreatment with *p*-CPA (400mg/kg) altered specific behaviors within the stereotypy component without altering the Composite Stereotypy Score itself. Gnaw was augmented while both Nod and Rear-gnaw were suppressed. Neither the hyperactivity, nor the hyperreactivity components of the Apo behavioral effects was affected by *p*-CPA pretreatment. *p*-CA pretreatment(10.4mg/kg) had similar effects on the stereotypy component as *p*-CPA(400mg/kg) except *p*-CA did not augment Gnaw. Also, unlike *p*-CPA, *p*-CA augmented the hyperactivity and, to a lesser extent, the hyperreactivity components of the Apo behavioral effect.

Pretreatment with low doses of *p*-CPA (250mg/kg) or *p*-CA (6.4mg/kg), like their high dose counterparts, also altered different aspects of the Apo behavioral effect. However, there were not as many changes. Thus, pretreatment with *p*-CPA (250mg/kg) only suppressed Rear-gnaw. This could be contrasted with relatively more changes with pretreatment with *p*-CA (6.4mg/kg). This not only suppressed Rear-gnaw, it also augmented measures of hyperactivity and especially those of hyperreactivity.

V. DISCUSSION

p-CPA and *p*-CA are both potent 5-HT depletors (at three days) but their mechanisms of action are very different. However, behavioral studies to date have only revealed similarities. In this study, through a biochemical challenge with Apo, it has been possible to differentiate behaviorally the subtle effects of the mechanisms of action of *p*-CPA and *p*-CA. This study also presents a more comprehensive paradigm for the study of the behavioral effects of Apo.

A. The Effects of Apo on Behavior

Administration of Apo(5mg/kg) to a saline animal produced heightened activity, stereotyped behaviors and heightened reactivity responses. The heightened locomotor response (increased Event Count, Duration Probability of Bout Locomotion; the Number of line crosses per minute of locomotion) was consistent with previous findings (Fray et al., 1980; Ljungberg & Ungerstedt, 1977a, 1978). However, the exact magnitude was difficult to compare because of different methodologies and equipments used in the studies. Finally, it is of interest to note that the rate of locomotion of the saline-Apo group remained very high during Trial 3 at a point in time where the saline control group was quite inactive. Since the animal was alone in the test apparatus in Trial 3, it suggest that the hyperactivity seen is not due to any social facilitative effect of the presence of the non-injected rat carrying over from the SOCIAL to the ALONE trials.

Apo introduced five new behaviors : Head-down, Nod, Gnaw, Rear-gnaw, and Jump. Head-down, although having a very different behavioral topography (Figure 1) from other stereotypic behaviors (Figure 2 to 4) may be considered as an integral part of the Apo behavioral effect. Szechtman, Ornstein, Teitelbaum, and Golani (1982) described a phenomenon of "snout contact fixation" whereby "the apomorphine-treated rats...maintained uninterrupted snout-to-surface contact, [actually touching or was at most a few millimeters away from a surface] from about two minutes after injection to shortly before grooming[signalling end of drug effect]" (p.389). This was not unlike the description of Head-down (Table 1) and its temporal expression in this study (Figure 1). Szechtman et al. suggested that this maintenance of snout-to-surface contact may be a fundamental aspect of the behavioral actions of Apo. Fray et al.(1980) also had a category Head-down. However, using percentage-of-animals as their dependent measure, they showed a clear dose-response effect rather than a time-dependent effect. These researchers also stated that Head-down was a significant behavior in the differentiation of dosage effects. In summary, although Head-down has not usually been considered in the literature as a component of stereotypic behavior, it is nevertheless an important aspect of the Apo behavioral effect.

The behavioral category Nod, as characterized in this study, may be similar to that of licking -which has been judged as an intermediate form of stereotypy in the rating scales used for Apo-induced stereotypy (Costall & Naylor, 1973; Ernst, 1966; Szechtman et al., 1982). Due to the nature of the test apparatus (opaque black box) and the observation angle (overhead view), the actual protusion of the rat's tongue could not be ascertained in this study. It is also not definitive from the literature whether other researchers have been able to see the actual protusion of the rat's tongue when licking is scored. If Nod were indeed licking, then the predominance of Nod in the saline-Apo (5mg/kg) group would not be consistent with previous findings. Both Fray et al.(1980) and Ljungberg and Ungerstedt (1977a) found gnawing -the more extreme stereotypic response- to be the predominant behavior at comparable dosages. For the saline-Apo group, gnawing was at a minimal level (Figure 3). This discrepancy may be due to the difference in apparatus used as well as behaviors coded. Ljungberg and Ungerstedt used a wooden floor (of comparable size to that used in this study) that had 2.5-cm diameter holes spaced 4.5 cm. apart and coded only gnawing -licking was not coded. Fray et al. used a wire grid box and recorded both gnawing and licking. Both of these apparatus provide better surfaces for inducing gnawing than the solid wooden floor used in this study. Ljungberg and Ungerstedt (1977b) indeed reported that gnawing was greatly suppressed when the holes were covered - a condition that approximated the one in this study. Since Ljungberg and Ungerstedt did not have a category for licking, the possibility that licking might predominate in that situation could not be ascertained. This raises the question concerning the relationship between the behaviors: Nod and Gnaw. The results from these two studies and those from this present one would suggest that administration of Apo(5mg/kg) produces either a predominance of Nod-lick or Gnaw depending on the test apparatus used. However, since *p*-CPA(400mg/kg) pretreatment in this study did induce a high proportion of gnawing, the situation is more complicated. This last result would suggest that the test apparatus used in this study can induce gnawing reliably only with the inhibitory effect of 5-HT removed. In conclusion, these findings support Ljungberg and Ungerstedt (1977b)'s suggestion that gnawing was less "compulsive" than in the usual definition of stereotypy because its expression can be modified by environmental manipulations.

Rear-gnaw, gnawing while the animal is rearing, has not been specifically assessed in the literature. Szechtman et al.(1982) did provide the opportunity for this behavior (by placing a small Plexiglas block glued to corners halfway up the test box) but the occurrence of gnawing-on-the-block was assessed as part of other oral activities (such as licking, gnawing-on-the-floor) and was not recorded separately. Thus a direct comparison of results was not possible. The significant proportion of time spent (as compared to all other groups) in Rear-gnaw in the saline-Apo group was not correlated with an increased proportion of time spent in Rear. Furthermore, even when the Duration Probabilities of Rear and Rear-gnaw were summed for the saline-Apo group, the total was still not significantly different from all the other groups. In fact, there was a tendency for the saline-Apo group to spend less time rearing (Rear and Rear-gnaw combined) than the other groups(Appendix A,Table 3,9). It would be of interest to investigate the effect on Rear-gnaw if better gnawing opportunities (such as placing blocks of wood on the side of the test apparatus as in Szechtman et al.'s study) were provided. In summary, the saline-Apo group tended to spend less time in rearing activities, but a significant proportion of that time was spent in Rear-gnaw.

Jumping was inconsistently elicited from the saline-Apo group. However, the clear potentiation of jumping by both *p*-CPA pretreatment groups suggest that jumping may be considered as another component of the Apo behavioral effect. In addition, Weissman (1971) has been able to reliably elicit cliff jumping - jumping off a high platform - from rats administered Apo(1mg/kg,i.v.). The role of DA in this behavior is unclear as DA, amphetamine, or nialaminde together with L-DOPA have been unable to elicit a similar response in that study. Although cliff jumping and upward jumping (in this study) can be viewed as different behaviors, the difference may be only one of apparatus. Lal

(1975) argued that without the confines of the walls (of the test apparatus), upward jumping and cliff jumping cannot be distinguished. However, the upward jumping as elicited in this study does require greater energy output by the animal than cliff jumping (as in Weissman's paradigm) because upward jumping is jumping against gravity. It would be of interest to run the same animals through both paradigms in order to see if there is any correlation between the frequency scores obtained. If both kind of jumping can be considered as forms of active escape behavior (Gage & Olton, 1975), then upward jumping in an animal might indicate greater need to escape than cliff jumping in the same animal because of the inherent extra energy requirement. The expectation is that if the degree of aversiveness of the environment can be manipulated, one would see a preference for cliff jumping in the mild aversive situation.

Apo administration, when compared to the saline control, significantly decreased Sniff, Inactive, Self-groom, and all social behaviors. These results were expected, although not previously documented by others. The increased time spent in locomotor activity plus the introduction of stereotypic behaviors all contributed to the decreased Event Count, Event Duration, and Duration Probability of the above behaviors. These results suggest that Apo administration has disrupted the normal pattern of investigative and social affiliative behaviors seen in a saline rat under the present testing paradigm. The Apo animal paid less attention to its environment (less Sniff) and less attention to social cues (less social behaviors) than its saline counterpart. These results cannot be explained by the process of habituation because there were no increases in time spent in Inactive, or Self-groom coupled with a decrease in time spent in Locomote - the pattern that was seen in animals that had been habituated to the test apparatus (Beck & Chow, unpublished data). In fact, there was a reverse pattern of increased locomotor activity together with decreased inactivity and self-grooming as well as decreased sniffing and social affilitative behaviors. This specific pattern of decreased sniffing and social affilitative behaviors seen in the Apo animal is similar to that found by File and Hyde (1978) in undrugged animals tested in a unfamiliar test chamber under high illumination. Their interpretation was that the high level of anxiety (the high illumination and the novel test chamber) is incompatible with exploration and social behaviors. The results from this study suggest that Apo administration, by disrupting the inherent balance between the 5-HT and DA systems, can also produce a similar pattern of decreased exploration and social interaction. An analogus interpretation can be made that the hyperactivity and stereotypy exhibited by the Apo animal were not compatible with normal exploration and social interactive behaviors.

In summary, Apo administration produced effects on locomotor and stereotypic activities that were in general agreement with the existing literature. Effects on explorative and social interactive behaviors were expected although have not been previously documented. Finally, although the measures of hyperreactivity were not significant, the strong potentiation seen in the *p*-CA pretreatment groups suggest that hyperreactivity may be considered as another component of the Apo behavioral effect.

B. Comparison of p-CPA and p-CA Effects on Apo

Neither dosage of *p*-CPA caused a significant potentiation of Apo-induced hyperactivity. This result was not expected. It is inconsistent with the finding of potentiation by Grabowska et al.(1973). However, pretreatment with both dosages of *p*-CA did significantly potentiate the Apo-induced hyperactivity as expected, confirming the findings of Grabowska and Michaluk (1974). The potentiation was in the form of greater intensity - increased number of line crosses while the amount of time spent in locomotion remained the same. This potentiation was only evident in the ALONE condition. During the SOCIAL condition, while the saline-Apo group became much more hyperactive (than in the ALONE condition), the locomotor activity of the *p*-CA pretreatment groups remained the same. The failure of the SOCIAL condition to produce a facilitation of locomotor activity in the *p*-CA groups may reflect a ceiling effect : the heightened locomotor activity was already at maximum during the ALONE condition. Finally, as expected, *p*-CA pretreatment(high dose, 10.4mg/kg) was significantly more hyperactive than its *p*-CPA counterpart (400mg/kg) in both ALONE and SOCIAL conditions. This potentiation had two aspects : the *p*-CA group had a increased number of line crosses as well as a decreased Event Duration of Bout Locomotion.

The potentiation of Apo-induced hyperreactivity by the *p*-CA pretreatment was expected. *p*-CA pretreatment (both doses) significantly increased Total Jump in both the ALONE and SOCIAL conditions when compared to all other groups except *p*-CPA(250mg/kg). Furthermore, the low dose of *p*-CA(6.4mg/kg) tended to be more hyperreactive than the high dose(10.4mg/kg). This trend was not expected. This suggests that there is a inverted-U shape relationship between the level of 5-HT depletion and level of Apo-induced hyperreactivity. Finally, the role of the hyperreactivity response in the heightened activity of the *p*-CA pretreated groups is not clear. The findings suggest that the two components are related since they co-exist in the same animals. However, it is not possible to assign causality from the data in this study.

Pretreatments with either *p*-CPA or *p*-CA suppressed both Nod and Rear-gnaw of the Apo-induced stereotypy. These results were not expected. However, *p*-CPA pretreatment did significantly augment Gnaw. Since gnawing is considered a extreme form of Apo-induced stereotypy, the *p*-CPA suppressive efffects on Nod and Rear-gnaw together with its potentiating effect on Gnaw can be viewed as a shift from a mild form to a more severe form of stereotypy. Thus, the overall *p*-CPA effect on Apo-induced stereotypy could be considered as one of potentiation. This extends the finding of Weiner et al.(1975) that the presence of the 5-HT system suppresses Apo-induced stereotypy in the guinea pig as well as the rat.

The situation with *p*-CA pretreatment was quite different : *p*-CA did not augment Gnaw. However, *p*-CA pretreatment did result in potentiation of hyperactivity. This potentiation together with the suppressive effects on stereotypy may be viewed as a form of behavioral incompatibility. Robbins & Iversen (1973) found that exploratory behavior was incompatible with very high rates of locomotor activity induced by amphetamine. Similarily, stereotypic behaviors such as Nod and Rear-gnaw may also be incompatible with the very high rate of locomotor activity induced by *p*-CA pretreatment. However, it is not possible to state from these results to what extent, if any, *p*-CA pretreatment had a direct inhibiting effect on Apo-induced stereotypic behaviors.

Although *p*-CPA and *p*-CA pretreatments did affect different aspects of Apo-induced behaviors, the underlying causes of these differences are not clear based on the findings from this study. The question remains : why did the *p*-CPA pretreatment differentially potentiate Apo-induced stereotypy while the *p*-CA pretreatment differentially potentiated Apo -induced hyperactivity and hyperreactivity? One possibility is that there is a difference in the pattern of depletion of 5-HT in the various areas of the brain caused by *p*-CPA and *p*-CA. If *p*-CA preferentially depleted 5-HT in the nucleus accumbens and *p*-CPA preferentially depleted 5-HT in the striatum, then one might attribute the results from this study to selective differential depletion. However, *p*-CA has been reported to cause the greatest depletion of 5-HT in the striatum (Kohler et al., 1978; Sanders-Bush, Bushing, & Sulser, 1975) or to cause no depletion at all (Dewhurst & McKim, 1980). If striatal 5-HT were indeed preferentially depleted by *p*-CA, the behavioral expectation would have been potentiation of stereotypy and not hyperactivity. Finally, to date, there has not been any evidence to suggest that *p*-CPA differentially blocks tryptophan hydroxylase at discrete brain regions. Thus the differential results of *p*-CPA and P-CA cannot be attributed to prefential depletion of 5-HT by either drug.

Another approach to this question is to examine studies that have focused specifically on the differentiation of the Apo induced hyperactivity and stereotypy effects. Both the noradrenaline (NA) and acetycholine (Ach) systems have been cited as modulators on these two aspects of the Apo behavioral syndrome. In addition, specific neuroleptics (DA receptor blockers) have been used to differentially block either the hyperactivity or the stereotypy components. The alpha-adrenergic blocker phenoxybenzamine has been shown to suppress the hyperactivity component (Maj, Grabowska, & Gajda, 1972) as well as to induce a qualitative shift in the expression of stereotypic behavior - from intense sniffing to biting/gnawing (Mogilnicka & Braestrup, 1976). These results suggest that the presence of NA has opposite effects on hyperactivity and stereotypy : augumenting/facilitating the former and suppressing the latter. The role of NA can be ruled out as a possible explanation for the differential effects of *p*-CPA and *p*-CA found in this study. Both *p*-CPA and *p*-CA have not been shown to have any significant effect on the NA system at three days (Koe & Weissman, 1966; Dewhurst & McKim, 1980; Kohler et al., 1978).

Ach agonists arecoline and eserine have been shown to reduce the hyperactivity induced by administration of DA into the nucleus accumbens (Costall, Hui, & Naylor, 1979). Anticholinergics scopolamine and benztropine have been shown to greatly enhance gnawing in mice after Apo administration (Scheel-Kruger, 1970). These results suggest that the presence of Ach has suppressive effects on both hyperactivity and stereotypy. The role of Ach is similar to that of 5-HT on these two aspects of dopaminergic functions. Ach can also be ruled out as a possible explanation for the results of *p*-CPA and *p*-CA because the Ach effects do not differentiate the components of hyperactivity and stereotypy.

Neuroleptics having high incidences of extrapyramidal side effects - metoclopramide, haloperidol, and chlorpromazine - have been shown to block Apo-induced gnawing at dosages where Apo-induced locomotor activity is not affected (Ljungberg & Ungerstedt, 1978). In the same study, neuropletics having low incidences of extrapyramidal side effects - thioridazine, clozapine, and sulpiride - have been shown to block Apo-induced locomotor activity without affecting the gnawing component. Costall & Naylor (1976) reported a similar pattern of results for the specific antagonism of locomotor activity (induced by injection of DA into the nucleus accumbens) by haloperidol and a relative lack of effect (20 to 50 times less potent) of clozapine, sulpiride, and thioridazine.

The finding of differential effects of neuroleptics on Apo-induced hyperactivity and stereotypy best parallel the results of *p*-CPA and *p*-CA in this study. After discounting both the differential antagonism of the DA mesolimbic and striatal pathways as well as a differential involvement of NA or Ach as possible explanations of their data, Ljungberg & Ungerstedt (1978) concluded that their findings were consistent with the concept of differential antagonism of two kinds of DA receptors (DAi and DAe). Cools (1977) postulated the existence of two DA receptors as well as two 5-HT systems and the complex interactions among these four systems. Briefly, Cools suggested that there are two 5-HT systems: one, originating from the medial raphe nuclei and terminating in the substantia nigra, and the other, originating from the dorsal raphe and terminating in the striatum. The medial 5-HT system inhibits the DAi-system (suppression of this DA system produces enhanced locomotor activity). The dorsal 5-HT system acts in concert with the DAe system (stimulation of this DA system produces enhanced locomotor activity). Lastly, stereotypied gnawing is postulated to be the result of simultanous activation of the DAe and suppression of the DAi systems. However, in order to explain the effects of *p*-CPA and *p*-CA in this study, one would still have to postulate a differential depleting action in these two 5-HT systems. Confirmation of such a hypothesis would have to await the analysis of neurochemicals in the discrete brain regions.

In summary, the potentiation of Apo-induced hyperactivity by *p*-CA and of Apo-induced stereotypy by *p*-CPA confirmed previous findings. As well, the potentiation of Apo-induced hyperreactivity by *p*-CA was expected although not previously documented. However, the lack of potentiation of Apo-induced hyperactivity by *p*-CPA and of Apo-induced stereotypy by *p*-CA were inconsistent with previous findings. Finally, although the study showed that *p*-CPA and *p*-CA can be differentiated in their effects on the Apo-induced behavioral syndrome, the underlying cause of this difference cannot be determined at this point.

C. Critique of paradigm used

In addition to the primary purpose of differentiating the behavioral effects of *p*-CPA and *p*-CA, the present study attempted to present an alternative paradigm for the assessment of the Apo behavioral effect.

This paradigm included a single injection schedule, a detailed behavioral log, the use of real-time sampling, the use of mutually exclusive categories, the recording of both the onset and offset of each behavior, the use of more than one dependent measure for each behavior and the use of more than one testing condition. This paradigm is similar to that used by Fray et al. (1980), but there are important differences. Although they used an extensive behavioral list, they only used 10-second interval sampling with 10-minute intersample intervals and non-exclusive categories (that is, more than one behavior can be recorded during any one 10-second interval). Their dependent measure for locomotor activity was photocell counts; for the other measures it was percentage-of-animals exhibiting the particular behavior in question. These differences proved to be crucial for this study. The most important difference was the use of more than one dependent measure per behavior. The exclusive use of a frequency measure (as in Fray et al.) would have missed many of the differences among *p*-CPA, *p*-CA and Apo groups (Table 3,4,5). Both Event Duration and Duration Probability were important discriminative measures in dissociating these drug effects. Similarily, the use of both the rate of locomotion (Number of line crosses per minute of locomotion) as well as the absolute Number of line crosses were crucial in dissociating the qualitative difference between the hyperactivity potentiated by *p*-CPA from that potentiated by *p*-CA. Both groups had spent equal amounts of time in locomotion but the *p*-CA pretreated group ran faster than the *p*-CPA group (Appendix A,Table 1,14). Finally, the use of the rate of locomotion was crucial in highlighting the hyperactivity response (Figure 5) in the saline-Apo group especially during Trial 3. If just the absolute number of line crosses were used , this effect would have been obscured.

As with Fray et al., the use of specific behavioral categories rather than a rating scale for the assessment of Apo-induced stereotypy was also crucial. Pretreatment with *p*-PCA modified only specific behaviors within the Apo-induced stereotypy component without altering the overall Composite Score. The use of a rating scale in this study would have obscured this effect.

Lastly, the use of the social condition served as an important adjunct to the traditional open field alone paradigm. Not only was the social condition another stressor, but it helped to elicit the hyperreactivity component of the Apo response. Although at the dosage of Apo used (5mg/kg), the jumping response was not significantly different from zero, the clear potentiation of that response by the *p*-CA pretreatments indicate that it should be considered as part of the Apo behavioral syndrome.

In summary, the use of this paradigm elicited qualitative aspects of the Apo-induced hyperactivity as well as focused on specific behaviors within the Apo-induced stereotypy. The inclusion of two testing condition elicited a possible third component of the Apo behavioral syndrome - hyperreactivity.

VI. REFERENCES

Anden, N-E., Rubenson, A., Fuxe, K., & Hokfelt, T. Evidence for dopamine receptor stimulation by apomorphine. Journal of Pharmacy and Pharmacology, 1967, 19, 627-629.

Baldessarini, R.J., Amatruda, T.T., Griffith, F.F., & Gerson, S. Differential effects of serotonin on turning and stereotypy induced by apomorphine. Brain Research, 1975, 93, 158-163.

Bliss, E.L. Ailion, J., & Zwanziger, J. Metabolism of norepinephrine, serotonin, and dopamine in the rat brain with stress. Journal of Pharmacology and Experimental Therapeutics, 1968, 164, 122-134.

Brady, J.V. & Nauta, W.J.H. Subcortical mechanisms in emotional behavior: affective changes following septal forebrain lesions in the albino rat. Journal of Comparative and Physiological Psychology, 1953, 46, 339-346.

Cohen, J. A coefficient of agreement for nominal scales. Educational and Psychological Measurement, 1960, 20, 37-46.

Cools, A.R. Basic considerations on the role of concertedly working dopaminergic, GABA-ergic, cholinergic and serotonergic mechanisms within the striatum and nucleus accumbens in locomotor activity, stereotyped gnawing, turning and dyskinetic activities. In E. Ellinwood (Ed.), Advances in Behavioral Biology (Vol. 21). New

York : Plenum Press, 1977.

Costall, B., Hui, S-C.G., & Naylor, R.Y. Hyperactivity induced by injection of dopamine into the accumbens nucleus : actions and interactions of neuroleptics, cholinomimetric and cholinolytic agents. Neuropharmacology, 1979, 18, 661-665.

Costall, B. & Naylor, R.J. On the mode of action of apomorphine. European Journal of Pharmacology, 1973, 21, 350-361.

Costall, B. & Naylor, R.J. The behavioral effects of dopamine applied intracerebrally to areas of the mesolimbic system. European Journal of Pharmacology, 1975, 32, 87-92.

Costall, B. & Naylor, R.J. Antagonism of the hyperactivity induced by dopamine applied intracerebrally to the nucleus accumbens septi by typical neuroleptics and by clozapine, sulpiride and thioridazine. European Journal of Pharmacology, 1976, 35, 161-168.

Costall, B., Naylor, R.J., & Neumeyer, J.L. Dissociation by the aporphine derivatives of the stereotypic and hyperactivity responses resulting from injections into the nucleus accumbens septi. Journal of Pharmacy and Pharmacology, 1975, 27, 875-877. (a)

Costall, B., Naylor, R.J., & Neumeyer, J.L. Differences in the nature of the stereotyped behaviour induced by aporphine derivatives in the rat and in their actions in extrapyramidal and mesolimbic brain areas. European

Jouranl of Pharmacology, 1975, 31, 1-16 .(b)

Dewhurst, W.G. & McKim, H.R. Pharmacological effects of p-chloroamphetamine with respect to current amine hypotheses of affective disorders. Neuropsychobiology, 1980, 6, 66-71.

Eckman, J., Meltzer, J.D., & Latane, B. Gregariousness in rats as a function of familiarity of environment. Journal of Personality and Social Psychology, 1969, 11, 107-114.

Ernst, A.M. Mode of action of apomorphine and dexamphetamine on gnawing compulsion in rats. Psychopharmacologia, 1967, 10, 316-323.

Ernst, A.M. & Smelik, P.G. Site of action of dopamine and apomorphine on compulsive gnawing behavior in rats. Experientia, 1966, 22, 837-838.

Fibiger, H.C. & Campbell, B.A. The effects of p-chlorophenylalanine on spontaneous locomotor activity in the rat. Neuropharmacology, 1971, 10, 25-32.

File, S.E. & Hyde, J.R.G. Can social interaction be used to measure anxiety? British Journal of Pharmacology, 1978, 62, 19-24.

File, S.E., Hyde, J.R.G., & MacLeod, N.K. 5,7-dihydroxytryptamine lesions of dorsal and medial raphe nuclei and performance in the social interaction test of anxiety and in a home-cage aggression test. Journal of Affective Disorders, 1979, 1, 115-122.

File, S.E. & Peet, L.A. The sensitivity of the rat corticosterone response to environmental manipulatioins and to chronic chlordiazepoxide treatment. Physiology and Behavior, 1980, 25, 753-758.

File, S.E. & Pope, J.H. Social interaction between drugged and undrugged rats. Animal Learning and Behavior, 1974, 2, 161-164.

Fray, P.J., Sahakian, B.J., Robbins, T.W., Koob, G.F., & Iversen, S.D. An observational method for quantifying the behavioral effects of dopamine agonists: constrasting effects of d-amphetamine and apomorphine. Psychopharmacology, 1980, 69, 253-259.

Gage, F.H. & Olton, D.S. Hippocampal influence on hyperreactivity induced by septal lesions. Brain Research, 1975, 98, 311-325.

Grabowska, M. Influence of apomorphine on brain serotonin turnover rate. Pharmacology Biochemistry and Behavior, 1975, 3, 589-591.

Grabowska, M. & Anden, N-E. Apomorphine in the rat nucleus accumbens: effects on the synthesis of 5-hydroxytryptamine and noradrenaline, the motor activity and the body temperature. Journal of Neural Transmission, 1976, 38, 1-8.

Grabowska, M., Antkiewicz, L., Maj, J., & Michaluk, J. Apomorphine and central serotonin neurons. Polish Journal of Pharmacology and Pharmacy, 1973, 25, 29-39.

Grabowska, M. & Michaluk, J. On the role of serotonin in apomorphine-induced locomotor stimulation in rat.

Pharmacology Biochemistry and Behavior ,1974, 2, 263-266.

Grabowska, M., Przewlocki, R., & Smialowska, M. On the direct or indirect influence of apomorphine on central serotonin neurons. Journal of Pharmacy and Pharmacology, 1976, 28, 64-65.

Harvey, J.A., McMaster, S.E., & Yunger, L.M. p-chloroamphetamine: selective neurotoxic action in brain. Science, 1975, 187, 841-843.

Jequier, E., Loverberg, W., & Sjoerdsma, A. Trytophan hydroxylase inhibition: the mechanism by which *p*-CPA depletes rat brain serotonin. Molecular Pharmacology, 1967, 3, 274-278.

Kelly, P.H., Seviour, P.W., & Iversen, S.D. Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. Brain Research, 1975, 94, 507-522.

Koe, B.K. & Weissman, A. p-chlorophenylalanine: a specific depletor of brain serotonin. Journal of Pharmacology and Experimental Therapeutics, 1966, 154, 499-516.

Kohler, C., Ross, S.B., Srebro, B., & Orgen, S-O. Long-term biochemical and behavioral effects of p-chloroamphetamine in the rat. Annals of New York Academy of Science, 1978, 305, 645-663.

Korf, J. & Kuiper, H.E. Induction of bizarre behavior in rats by *p*-CA, a serotonin depletor, after repeated drug administration. Psychopharmacologia, 1971, 21, 328-337.

Lal, H. Narcotic dependence, narcotic action and dopamine receptors. Life Science, 1975, 17, 483-496.

Ljungberg, T. & Ungerstedt, U. Different behavioral patterns induced by apomorphine: evidence that the method of administration determines the behavioral response to the drug. European Journal of Pharmacology, 1977, 46, 41-50. (a)

Ljungberg, T. & Ungerstedt, U. Apomorphine-induced locomotion and gnawing: evidence that the experimental design greatly influences gnawing while locomotion remains unchanged. European Journal of Pharmacology, 1977, 46, 147-151. (b)

Ljungberg, T. & Ungerstedt, U. Classification of neuroleptic drugs according to their ability to inhibit apomorphine-induced locomotion and gnawing: evidence for two mechanisms of actions. Psychopharmacology, 1978, 56, 239-247.

Maj, J., Grabowska, M., & Gajda, L. Effects of apomorphine on motility in rats. European Journal of Pharmacology, 1972, 17, 208-214.

McDonald, A.L. & Heimstra, N.W. Social influences on the response to drugs. V. Modification of behavior of non-drugged rats by drugged. Psychopharmacologia, 1965, 8, 174-180.

McKenzie, G.M. Role of the tuberculum olfactorium in stereotyped behavior induced by apomorphine in the rat. Psychopharmacologia, 1972, 23, 212-219.

Messing, R.B., Phebus, L., Fisher, L.A., & Lytle, L.L. Effects of *p*-CA on locomotor activity and brain 5-hydroxyindoles. Neuropharmacology, 1976, 15, 157-163.

Meyerson, B.J. & Hoglund, A.U. Exploratory and socio-sexual behavior in the male laboratory rat: a methodological approach for the investigation of drug action. Acta Pharmacologica et Toxicologica, 1981, 48, 168-180.

Miczek, K.A. Intraspecies aggression in rats: effects of d-amphetamine and chlordiazepoxide. Psychopharmacologia, 1974, 39, 275-301.

Miczek, K.A., Altman, J.L., Appel, J.B., & Boggan, W.O. Para-chlorophylalanine, serotonin and killing behavior. Pharmacology Biochemistry and Behavior, 1975, 3, 355-361.

Mogilnicka. E. & Braestrup, C. Noradrenergic influence on the stereotyped behavior induced by amphetamine, phenethylamine and apomorphine. Journal of Pharmacy and Pharmacology, 1976, 28, 253-255.

Nyback, H., Schubert, J., & Sedvall. G. Effects of apomorphine and pimozide on synthesis and turnover of labelled catecholamines in mouse brain. Journal of Pharmacy and Pharmacology, 1970, 22, 622-624.

Pijnenburg, A.J.J., Honig, W.M.M., van der Heyden, J.A.M., & van Rossum, J.M. Effects of chemical stimulation of the mesolimbic dopamine system upon locomotor activity. European Journal of Pharmacology, 1976, 35, 45-58.

Pijnenburg, A.J.J. & van Rossum, J.M. Stimulation of locomotor activity following injection of dopamine into the nucleus accumbens. Journal of Pharmacy and Pharmacology, 1973, 25, 1003-1005.

Robbins, T. & Iversen, S.D. A dissociation of the effects of d-amphetamine on locomotor activity and exploration in rats. Psychopharmacologia , 1973, 28, 155-164.

Roos, B-E. Decrease in homovanillic acid as evidence for dopamine receptor stimulation by apomorphine in the neostriatum of the rat. Journal of Pharmacy and Pharmacology, 1969, 21, 263-264.

Rostrosen, J., Angrist, B.M., Wallach, M.B., & Gershon, S. Absence of serotonergic influence on apomorphine-induced stereotypy. European Journal of Pharmacology, 1972, 20, 133-135.

Saavedra, J.M., Brownstein, M., & Palkovits, M. Serotonin distribution in the limbic system of the rat. Brain Research, 1974, 79, 431-436.

Sahakian, B.J., Robbins, T.W., Morgan, M.J., & Iversen, S.D. The effects of psychomotor stimulants on stereotypy and locomotor activity in socially-deprived and control rats. Brain Research, 1975, 84, 195-205.

Sanders-Bush, E., Bushing, J.A., & Sulser, F. Long-term effects of p-chloroamphetamine and related drugs on central serotonergic mechanisms. Journal of Pharmacology and Experimental Therapeutics, 1975, 192, 33-41.

Sanders-Bush, E., Bushing, J.A., & Sulser, F. Long-term effects of *p*-CA on tryptophan hydroxylase activity and on the levels of 5-hydroxytryptamine and 5-hydroxyindole acetic acid in brain. European Journal of Pharmacology, 1972, 20, 385-388.

Scheel-Kruger, J. Central effects of anticholingeric drugs measured by the apomorphine gnawing test in mice. Acta Pharmacologica et Toxicologica, 1970, 28, 1-16.

Scheel-Kruger, J. & Hasselager, E. Studies of various amephetamines, apomorphine and clonidine on body temperature and brain 5-hydroxytryptamine metabolism in rats. Psychopharmacologia, 1974, 36, 189-202.

Seiden, L.S. & Dykstra, L.A. Psychopharmacology: a biochemical and behavioral appraoch. chap. 4. New York: van Nostrand Reinhold Company, 1977.

Seiden, L.S. & Dykstra, L.A. Psychopharmacology: a biochemical and behavioral appraoch. chap. 5. New York: van Nostrand Reinhold Company, 1977.

Sjoerdsma, A., Lovenberg, W., Engelman, K., Carpenter, W.T., Wyatt, R.J., & Gessa, G.L. Serotonin now: clinical implications of inhibiting its synthesis with *para*-chlorophenylalanine. Annals of Internal Medicine, 1970, 73, 607-629.

Sodersten, P., Berge, O.G., & Hole, K. Effects of p-chloroamphetamine and 5,7-dihydroxytryptamine on the sexual behavior of gonadectomized male and female rat. Pharmacology Biochemistry and Behavior, 1978, 9, 499-508.

Steranka, L.R., Barrett, R.J., & Sanders-Bush, E. Facilitation of sidman avoidance performance by p-chloroamphetamine: role of biogenic amines. Neuropharmacology, 1977, 16, 751-759.

Steranka, L.R., Sanders-Bush, E., & Barrett, R.T. Tolerance to p-chloroamphetamine's effects on Sidman avoidance performance and catecholamine metabolism. Neuropharmacology, 1977, 16, 761-769.

Szechtman, H., Ornstein, K., Teitelbaum, P., & Golani, I. Snout contact fixation, climbing and gnawing during apomorphine stereotypy in rats from two substrains. European Journal of Pharmacology, 1982, 80, 385-392.

Tagliamonte, A., Tagliamonte, P., Gessa, G.L., & Brodie, B.B. Compulsive sexual activity induced by p-chlorophenylalanine in normal and pinealectomized male rats. Nature, 1969, 166, 1433-1435.

Tanaka, C., Yoh, Y-J., & Takaori, S. Relationship between brain monoamine levels and sidman avoidance behavior in rats treated with tyrosine and trytophan hydroxylase inhibitors. Brain Research, 1972, 45, 153-164.

Tenen, S.S. The effects of p-chlorophenylalanine, a serotonin depletor, on avoidance acquisition, pain sensitivity and related behavior in the rat. Psychopharmacologia, 1967, 10, 204-219.

Thierry, A-M., Fekete, M., & Glowinski, J. Effects of stress on the metabolism of noradenaline, dopamine and serotonin (5-HT) in the central nervous system of the rat. II. Modifications of serotonin metabolism. European Journal of Pharmacology, 1968, 4, 384-389.

Van Praag, H.M. & Korf, J. 4-chloroamphetamines. Chance and trend in the development of new antidepressants. Journal of Clinical Pharmacology, 1973, 13, 3-14.

Voith, K. Supersensitivity to apomorphine in experimentally induced hypokinesia and drug-induced modifications of the apomorphine response. Psychopharmacology, 1980, 79, 247-254.

Vorhees, C.V. Facilitation of avoidance acquisition in rats produced by p-chlorophenylalanine or p-chloroamphetamine. Pharmacology Biochemistry and Behavior, 1979, 10, 569-576.

Vorhees, C.V., Schaeffer, G.J., & Barrett, R.J. p-chloroamphetamine: behavioral effects of reduced cerebral serotonin. Pharmacology Biochemistry and Behavior, 1975, 3, 279-284.

Weiner, W.J., Goetz, C., & Klawans, H.L. Serotonergic and antiserotonergic influences on apomorphine-induced stereotyped behavior. Acta Pharmacolgica et Toxicologica, 1975, 36, 155-160.

Weissman, A. Cliff jumping in rats after intravenous treatment with apomorphine. Psychopharmacologia, 1971, 21, 60-65.

VII. APPENDIX A : Tables of Mean Values

Table 1
Means (and SEM) of the Dependent Measures of LOCOMOTE of the Six Groups In ALONE, SOCIAL, and TOTAL Trials

EVENT COUNT:

Group[1]	Alone	Social	Total
1	18.4(2.0)	64.2(5.7)	41.3(3.5)
2	42.2(6.2)	61.1(8.7)	51.6(7.0)
3	41.7(6.3)	51.6(9.7)	46.7(7.1)
4	46.7(4.8)	59.7(5.8)	53.2(5.1)
5	51.2(3.3)	70.9(5.8)	61.1(4.1)
6	55.4(3.3)	69.1(7.8)	62.3(7.1)

EVENT DURATION(seconds):

Group	Alone	Social	Total
1	1.12(.16)	1.40(.05)	1.26(.09)
2	2.19(.12)	1.95(.16)	2.07(.13)
3	2.59(.23)	2.26(.20)	2.43(.21)
4	2.20(.18)	1.88(.14)	2.04(.15)
5	2.00(.16)	1.82(.12)	1.91(.13)
6	2.07(.18)	1.80(.14)	1.94(.15)

DURATION PROBABILITY:

Group	Alone	Social	Total
1	.077(.010)	.244(.020)	.161(.010)
2	.242(.030)	.305(.040)	.274(.030)
3	.277(.040)	.285(.030)	.281(.030)
4	.268(.030)	.299(.030)	.284(.030)
5	.269(.030)	.352(.040)	.311(.030)
6	.276(.030)	.321(.030)	.299(.030)

[1] group 1 = saline control
group 2 = saline-Apo(5mg/kg)
group 3 = p-CPA(400mg/kg)/Apo(5mg/kg)
group 4 = p-CPA(250mg/kg)/Apo(5mg/kg)
group 5 = p-CA(10.4mg/kg)/Apo(5mg/kg)
group 6 = p-CA(6.4mg/kg)/Apo(5mg/kg)

Table 2
Means (and SEM) of the Dependent Measures of REAR of the Six Groups In ALONE, SOCIAL, and TOTAL Trials

EVENT COUNT:

Group[1]	Alone	Social	Total
1	8.7(1.2)	11.6(1.0)	10.1(0.9)
2	4.7(1.4)	6.9(2.0)	5.8(1.7)
3	9.6(2.7)	12.8(4.1)	11.2(3.3)
4	10.3(2.8)	12.2(2.7)	11.3(2.7)
5	11.5(3.3)	11.5(3.2)	11.5(3.2)
6	9.0(1.9)	12.1(2.2)	10.6(2.0)

EVENT DURATION(seconds):

Group	Alone	Social	Total
1	1.52(0.34)	2.63(0.27)	2.07(0.25)
2	3.68(1.10)	4.57(1.30)	4.12(1.05)
3	5.58(1.70)	4.93(1.50)	5.26(1.56)
4	8.16(1.90)	6.55(1.30)	7.36(1.56)
5	4.70(1.10)	4.89(1.20)	4.79(1.10)
6	5.15(1.40)	5.28(1.20)	5.21(1.25)

DURATION PROBABILITY:

Group	Alone	Social	Total
1	.061(.008)	.086(.010)	.074(.007)
2	.086(.030)	.106(.030)	.096(.030)
3	.193(.060)	.198(.060)	.195(.060)
4	.243(.060)	.221(.060)	.232(.060)
5	.217(.070)	.192(.050)	.205(.060)
6	.168(.050)	.192(.050)	.180(.050)

[1] group 1 = saline control
group 2 = saline-Apo(5mg/kg)
group 3 = p-CPA(400mg/kg)/Apo(5mg/kg)
group 4 = p-CPA(250mg/kg)/Apo(5mg/kg)
group 5 = p-CA(10.4mg/kg)/Apo(5mg/kg)
group 6 = p-CA(6.4mg/kg)/Apo(5mg/kg)

Table 3
Means (and SEM) of the Dependent Measures of SNIFF of the Six Groups In ALONE, SOCIAL, and TOTAL Trials

EVENT COUNT:

Group[1]	Alone	Social	Total
1	34.6(2.8)	52.6(4.6)	43.6(3.1)
2	25.5(7.9)	28.1(7.1)	26.8(7.3)
3	13.1(3.2)	22.2(3.7)	17.6(3.0)
4	20.7(4.7)	31.6(6.3)	26.2(5.3)
5	24.6(5.9)	34.7(6.9)	29.7(6.2)
6	28.3(8.9)	36.2(8.3)	32.2(8.4)

EVENT DURATION(seconds):

Group	Alone	Social	Total
1	7.22(0.88)	2.07(0.16)	4.64(0.47)
2	2.38(0.29)	2.68(0.84)	2.49(0.53)
3	1.25(0.24)	1.95(0.28)	1.60(0.22)
4	1.83(0.35)	2.08(0.32)	1.95(0.29)
5	1.56(0.18)	2.19(0.23)	1.87(0.14)
6	1.93(0.27)	2.42(0.40)	2.18(0.30)

DURATION PROBABILITY:

Group	Alone	Social	Total
1	.481(.030)	.297(.030)	.389(.020)
2	.207(.070)	.196(.060)	.202(.070)
3	.053(.010)	.150(.030)	.102(.020)
4	.133(.040)	.206(.050)	.169(.040)
5	.124(.030)	.221(.030)	.172(.030)
6	.170(.050)	.226(.040)	.198(.040)

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[1] group 1 = saline control
group 2 = saline-Apo(5mg/kg)
group 3 = p-CPA(400mg/Kg)/Apo(5mg/kg)
group 4 = p-CPA(250mg/Kg)/Apo(5mg/kg)
group 5 = p-CA(10.4mg/Kg)/Apo(5mg/kg)
group 6 = p-CA(6.4mg/Kg)/Apo(5mg/kg)

Table 4
Means (and SEM) of the Dependent Measures of INACTIVE of the Six Groups In ALONE, SOCIAL, and TOTAL Trials

EVENT COUNT:

Group[1]	Alone	Social	Total
1	8.50(1.40)	0.13(0.10)	4.30(0.73)
2	0	0.03(0.03)	0.02(0.02)
3	0	0	0
4	0	0.13(0.13)	0.07(0.07)
5	0	0.07(0.07)	0.03(0.03)
6	0	0	0

EVENT DURATION(seconds):

Group	Alone	Social	Total
1	8.20(1.80)	0.12(0.12)	4.16(0.90)
2	0	0.48(0.48)	0.24(0.24)
3	0	0	0
4	0	0.08(0.08)	%[2]
5	0	%	%
6	0	0	0

DURATION PROBABILITY:

Group	Alone	Social	Total
1	.233(.040)	.001(.001)	.117(.020)
2	0	.001(.001)	.001(.001)
3	0	0	0
4	0	.001(.001)	<.001
5	0	<.001	<.001
6	0	0	0

[1] group 1 = saline control
group 2 = saline-Apo(5mg/kg)
group 3 = p-CPA(400mg/kg)/Apo(5mg/kg)
group 4 = p-CPA(250mg/kg)/Apo(5mg/kg)
group 5 = p-CA(10.4mg/kg)/Apo(5mg/kg)
group 6 = p-CA(6.4mg/kg)/Apo(5mg/kg)

[2] Event Duration not calculated when total duration was less than 0.5sec. in any one trial.

Table 5

Means (and SEM) of the Dependent Measures of SELF-GROOM of the Six Groups In ALONE, SOCIAL, and TOTAL Trials

EVENT COUNT:

Group[1]	Alone	Social	Total
1	2.40(0.63)	2.40(0.63)	2.50(0.42)
2	0	0.07(0.04)	0.03(0.02)
3	0	0.10(0.07)	0.05(0.04)
4	0.03(0.11)	0.13(0.13)	0.08(0.07)
5	0	0.03(0.03)	0.02(0.02)
6	0	0.07(0.07)	0.03(0.03)

EVENT DURATION(seconds):

Group	Alone	Social	Total
1	9.57(4.90)	3.63(2.80)	6.62(2.20)
2	0	%[2]	%
3	0	0.96(0.73)	0.48(0.37)
4	0	0.21(0.21)	0.11(0.11)
5	0	0.48(0.48)	0.24(0.24)
6	0	%	%

DURATION PROBABILITY:

Group	Alone	Social	Total
1	.129(.030)	.042(.010)	.086(.020)
2	0	<.001	<.001
3	0	.003(.002)	.002(.001)
4	<.001	.002(.002)	.002(.001)
5	0	.001(.001)	.001(.001)
6	0	<.001	<.001

---

[1] group 1 = saline control
group 2 = saline-Apo(5mg/kg)
group 3 = p-CPA(400mg/kg)/Apo(5mg/kg)
group 4 = p-CPA(250mg/kg)/Apo(5mg/kg)
group 5 = p-CA(10.4mg/kg)/Apo(5mg/kg)
group 6 = p-CA(6.4mg/kg)/Apo(5mg/kg)

[2] Event Duration not calculated when total duration was less than 0.5sec. in any one trial.

Table 6
Means (and SEM) of the Dependent Measures of HEAD-DOWN of the Six Groups In ALONE, SOCIAL, and TOTAL Trials

EVENT COUNT:

Group[1]	Alone	Social	Total
1	0.1(0.1)	0.2(0.1)	0.2(0.1)
2	21.7(5.3)	19.3(6.3)	20.5(5.6)
3	30.0(4.8)	22.9(3.7)	26.5(3.9)
4	31.5(3.0)	21.3(3.9)	26.4(3.1)
5	34.8(6.1)	23.2(4.0)	29.0(4.7)
6	34.5(7.0)	24.8(6.8)	29.7(6.6)

EVENT DURATION(seconds):

Group	Alone	Social	Total
1	0.24(.24)	%[2]	%
2	2.18(.37)	1.87(.38)	2.02(.35)
3	2.20(.25)	1.87(.19)	2.03(.17)
4	2.14(.15)	1.56(.19)	1.85(.15)
5	2.27(.40)	1.41(.29)	1.84(.34)
6	2.25(.55)	1.32(.31)	1.79(.35)

DURATION PROBABILITY:

Group	Alone	Social	Total
1	.001(.001)	<.001	<.001
2	.189(.040)	.112(.040)	.151(.040)
3	.201(.030)	.123(.020)	.162(.020)
4	.217(.020)	.112(.030)	.165(.020)
5	.256(.050)	.110(.020)	.183(.030)
6	.230(.040)	.116(.030)	.173(.030)

---

[1] group 1 = saline control
group 2 = saline-Apo(5mg/kg)
group 3 = p-CPA(400mg/kg)/Apo(5mg/kg)
group 4 = p-CPA(250mg/kg)/Apo(5mg/kg)
group 5 = p-CA(10.4mg/kg)/Apo(5mg/kg)
group 6 = p-CA(6.4mg/kg)/Apo(5mg/kg)

[2] Event Duration not calculated when total duration was less than 0.5sec. in any one trial.

Table 7
Means (and SEM) of the Dependent Measures of NOD of the Six Groups In ALONE, SOCIAL, and TOTAL Trials

EVENT COUNT:

Group[1]	Alone	Social	Total
1	0	0.03(0.03)	0.02(0.02)
2	7.60(2.80)	11.40(4.90)	9.50(3.80)
3	7.40(3.60)	3.40(1.60)	5.40(2.60)
4	7.70(3.40)	5.80(3.00)	6.80(2.90)
5	7.00(4.00)	5.20(3.70)	6.10(3.80)
6	8.20(3.50)	8.60(3.80)	8.40(3.50)

EVENT DURATION(seconds):

Group	Alone	Social	Total
1	0	%[2]	%
2	3.39(1.70)	2.55(1.26)	2.97(1.45)
3	0.74(0.35)	0.70(0.31)	0.72(0.29)
4	1.06(0.42)	0.96(0.35)	1.01(0.37)
5	1.07(0.48)	0.68(0.36)	0.87(0.41)
6	1.15(0.42)	1.13(0.49)	1.14(0.43)

DURATION PROBABILITY:

Group	Alone	Social	Total
1	0	<.001	<.001
2	.167(.070)	.166(.080)	.167(.080)
3	.062(.030)	.022(.010)	.042(.020)
4	.081(.040)	.058(.030)	.070(.030)
5	.073(.040)	.037(.020)	.052(.030)
6	.087(.030)	.076(.030)	.082(.030)

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[1] group 1 = saline control
group 2 = saline-Apo(5mg/kg)
group 3 = p-CPA(400mg/kg)/Apo(5mg/kg)
group 4 = p-CPA(250mg/kg)/Apo(5mg/kg)
group 5 = p-CA(10.4mg/kg)/Apo(5mg/kg)
group 6 = p-CA(6.4mg/kg)/Apo(5mg/kg)

[2] Event Duration not calculated when total duration was less than 0.5sec. in any one trial.

Table 8
Means (and SEM) of the Dependent Measures of GNAW of the Six Groups In ALONE, SOCIAL, and TOTAL Trials

EVENT COUNT:

Group[1]	Alone	Social	Total
1	0	0	0
2	0.97(0.52)	1.07(0.75)	1.02(0.62)
3	6.30(2.50)	5.80(2.90)	6.07(2.50)
4	1.20(0.77)	3.00(2.30)	2.12(1.50)
5	2.70(1.80)	2.20(1.50)	2.50(1.70)
6	2.10(2.00)	2.00(2.00)	2.03(2.00)

EVENT DURATION(seconds):

Group	Alone	Social	Total
1	0	0	0
2	0.57(0.31)	0.93(0.76)	0.75(0.52)
3	6.64(4.70)	3.87(2.50)	5.26(3.60)
4	0.78(0.60)	0.69(0.54)	0.74(0.57)
5	0.56(0.41)	0.37(0.29)	0.46(0.35)
6	0.16(0.16)	0.17(0.17)	0.17(0.17)

DURATION PROBABILITY:

Group	Alone	Social	Total
1	0	0	0
2	.011(.010)	.023(.020)	.017(.010)
3	.187(.100)	.163(.090)	.175(.100)
4	.036(.030)	.049(.040)	.043(.040)
5	.036(.030)	.025(.020)	.031(.020)
6	.027(.030)	.012(.010)	.019(.020)

[1] group 1 = saline control
group 2 = saline-Apo(5mg/kg)
group 3 = p-CPA(400mg/kg)/Apo(5mg/kg)
group 4 = p-CPA(250mg/kg)/Apo(5mg/kg)
group 5 = p-CA(10.4mg/kg)/Apo(5mg/kg)
group 6 = p-CA(6.4mg/kg)/Apo(5mg/kg)

Table 9
Means (and SEM) of the Dependent Measures of REAR-GNAW of the Six Groups In ALONE, SOCIAL, and TOTAL Trials

EVENT COUNT:

Group[1]	Alone	Social	Total
1	0	0.03(0.03)	0.02(0.02)
2	1.10(0.73)	1.03(0.64)	1.07(0.69)
3	0.47(0.40)	0.47(0.35)	0.47(0.34)
4	0.07(0.40)	0.33(0.27)	0.20(0.14)
5	0.13(0.10)	0.23(0.20)	0.18(0.15)
6	0.63(0.50)	0.20(0.17)	0.42(0.33)

EVENT DURATION(seconds):

Group	Alone	Social	Total
1	0	%[2]	%
2	5.40(3.70)	3.46(2.40)	4.43(3.00)
3	0.32(0.26)	0.66(0.42)	0.49(0.29)
4	%	0.15(0.15)	0.08(0.08)
5	0.08(0.08)	0.32(0.32)	0.20(0.20)
6	0.21(0.21)	0.12(0.12)	0.16(0.16)

DURATION PROBABILITY:

Group	Alone	Social	Total
1	0	<.001	<.001
2	.077(.050)	.046(.030)	.062(.040)
3	.004(.004)	.008(.007)	.006(.005)
4	<.001	.002(.002)	.001(.001)
5	.001(.001)	.003(.003)	.002(.002)
6	.009(.009)	.002(.002)	.005(.005)

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[1] group 1 = saline control
group 2 = saline-Apo(5mg/kg)
group 3 = p-CPA(400mg/kg)/Apo(5mg/kg)
group 4 = p-CPA(250mg/kg)/Apo(5mg/kg)
group 5 = p-CA(10.4mg/kg)/Apo(5mg/kg)
group 6 = p-CA(6.4mg/kg)/Apo(5mg/kg)

[2] Event Duration not calculated when total duration was less than 0.5sec. in any one trial.

Table 10
Means (and SEM) of the Dependent Measures of JUMP of the Six Groups In ALONE, SOCIAL, and TOTAL Trials

EVENT COUNT:

Group[1]	Alone	Social	Total
1	0	0	0
2	0.1(0.1)	1.8(1.3)	1.0(0.7)
3	0.3(0.3)	2.7(0.8)	1.5(0.5)
4	0.5(0.2)	3.3(1.4)	1.9(0.8)
5	2.1(1.3)	4.0(1.6)	3.1(1.4)
6	5.1(2.5)	6.9(2.1)	6.0(2.2)

EVENT DURATION(seconds):

Group	Alone	Social	Total
1	0	0	0
2	%[2]	0.04(0.03)	0.02(0.02)
3	%	0.11(0.04)	0.06(0.02)
4	%	0.15(0.08)	0.07(0.04)
5	0.13(0.32)	0.28(0.13)	0.21(0.11)
6	0.24(0.33)	0.36(0.11)	0.30(0.10)

DURATION PROBABILITY:

Group	Alone	Social	Total
1	0	0	0
2	<.001	.002(.001)	.001(.007)
3	<.001	.002(.001)	.001(.005)
4	<.001	.005(.003)	.003(.002)
5	.004(.003)	.008(.004)	.006(.004)
6	.012(.006)	.014(.005)	.013(.005)

[1] group 1 = saline control
group 2 = saline-Apo(5mg/kg)
group 3 = p-CPA(400mg/kg)/Apo(5mg/kg)
group 4 = p-CPA(250mg/kg)/Apo(5mg/kg)
group 5 = p-CA(10.4mg/kg)/Apo(5mg/kg)
group 6 = p-CA(6.4mg/kg)/Apo(5mg/kg)

[2] Event Duration not calculated when total duration was less than 0.5sec. in any one trial.

Table 11
Means (and SEM) of the Dependent Measures of GNAW+NOD of the Six Groups In ALONE, SOCIAL, and TOTAL Trials

EVENT COUNT:

Group[1]	Alone	Social	Total
1	0	0.03(0.03)	0.02(0.02)
2	8.60(2.90)	12.40(4.90)	10.50(3.80)
3	13.70(4.30)	9.20(2.80)	11.50(3.20)
4	8.90(3.60)	8.90(4.30)	8.90(3.70)
5	9.80(4.30)	7.40(3.80)	8.60(4.00)
6	10.20(4.50)	10.60(5.20)	10.40(4.80)

EVENT DURATION(seconds):

Group	Alone	Social	Total
1	0	%[2]	%
2	3.33(1.70)	2.77(1.30)	3.05(1.50)
3	6.88(4.60)	4.17(2.50)	5.52(3.50)
4	1.58(0.70)	1.39(0.60)	1.48(0.64)
5	1.31(0.58)	0.90(0.45)	1.10(0.55)
6	1.31(0.47)	1.10(0.48)	1.20(0.45)

DURATION PROBABILITY:

Group	Alone	Social	Total
1	0	<.001	<.001
2	.180(.070)	.188(.080)	.184(.080)
3	.249(.090)	.184(.090)	.217(.090)
4	.117(.050)	.107(.060)	.112(.050)
5	.109(.050)	.062(.030)	.086(.040)
6	.114(.050)	.088(.040)	.101(.050)

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[1] group 1 = saline control
group 2 = saline-Apo(5mg/kg)
group 3 = p-CPA(400mg/kg)/Apo(5mg/kg)
group 4 = p-CPA(250mg/kg)/Apo(5mg/kg)
group 5 = p-CA(10.4mg/kg)/Apo(5mg/kg)
group 6 = p-CA(6.4mg/kg)/Apo(5mg/kg)

[2] Event Duration not calculated when total duration was less than 0.5sec. in any one trial.

Table 12
Means (and SEM) of the Dependent Measures of GNAW+REAR-GNAW of the Six Groups In ALONE, SOCIAL, and TOTAL Trials

EVENT COUNT:

Group[1]	Alone	Social	Total
1	0	0.03(0.03)	0.02(0.02)
2	2.07(1.20)	2.10(1.30)	2.10(1.20)
3	6.80(2.50)	6.30(2.90)	6.50(2.50)
4	1.30(0.76)	3.30(2.50)	2.30(1.60)
5	2.90(1.90)	2.40(1.60)	2.60(1.80)
6	2.70(2.10)	2.20(2.20)	2.50(2.00)

EVENT DURATION(seconds):

Group	Alone	Social	Total
1	0	%[2]	%
2	2.95(1.90)	2.06(1.40)	2.50(1.60)
3	6.75(4.60)	4.11(2.50)	5.43(3.60)
4	0.78(0.60)	0.65(0.50)	0.71(0.55)
5	0.54(0.39)	0.51(0.34)	0.52(0.36)
6	0.37(0.25)	0.29(0.20)	0.33(0.22)

DURATION PROBABILITY:

Group	Alone	Social	Total
1	0	<.001	<.001
2	.089(.060)	.069(.050)	.079(.050)
3	.191(.100)	.171(.090)	.181(.100)
4	.036(.030)	.051(.040)	.043(.040)
5	.037(.030)	.028(.020)	.032(.030)
6	.036(.030)	.013(.010)	.025(.020)

[1] group 1 = saline control
group 2 = saline-Apo(5mg/kg)
group 3 = p-CPA(400mg/Kg)/Apo(5mg/kg)
group 4 = p-CPA(250mg/Kg)/Apo(5mg/kg)
group 5 = p-CA(10.4mg/Kg)/Apo(5mg/kg)
group 6 = p-CA(6.4mg/Kg)/Apo(5mg/kg)

[2] Event Duration not calculated when total duration was less than 0.5sec. in any one trial.

Table 13

Means (and SEM) of the Dependent Measures of COMPOSITE[1] STEREOTYPY of the Six Groups in ALONE, SOCIAL, and TOTAL Trials

EVENT COUNT:

Group[2]	Alone	Social	Total
1	0	0.07(0.07)	0.03(0.03)
2	9.70(3.10)	13.50(5.00)	11.60(3.90)
3	14.10(4.50)	9.70(2.70)	11.90(3.30)
4	9.00(3.60)	9.20(4.40)	9.10(3.70)
5	9.90(4.30)	7.60(3.80)	8.80(4.00)
6	10.90(4.50)	10.80(5.20)	10.90(4.80)

EVENT DURATION(seconds):

Group	Alone	Social	Total
1	0	%[3]	%
2	5.08(2.10)	3.58(1.50)	4.33(1.80)
3	6.88(4.60)	4.21(2.40)	5.55(3.50)
4	1.57(0.70)	1.35(0.57)	1.46(0.62)
5	1.30(0.58)	1.02(0.46)	1.16(0.51)
6	1.33(0.46)	1.10(0.48)	1.21(0.45)

DURATION PROBABILITY:

Group	Alone	Social	Total
1	0	<.001	<.001
2	.257(.080)	.234(.080)	.245(.080)
3	.253(.090)	.192(.090)	.223(.090)
4	.117(.050)	.109(.060)	.113(.050)
5	.110(.050)	.065(.030)	.087(.040)
6	.123(.050)	.090(.040)	.106(.050)

[1] Composite = Gnaw+Nod+Rear-gnaw

[2] group 1 = saline control
group 2 = saline-Apo(5mg/kg)
group 3 = p-CPA(400mg/kg)/Apo(5mg/kg)
group 4 = p-CPA(250mg/kg)/Apo(5mg/kg)
group 5 = p-CA(10.4mg/kg)/Apo(5mg/kg)
group 6 = p-CA(6.4mg/kg)/Apo(5mg/kg)

[3] Event Duration not calculated when total duration was less than 0.5sec. in any one trial.

Table 14
Means (and SEM) of the Additional Measures of LOCOMOTE of the Six Groups In ALONE, SOCIAL, and TOTAL Trials

Number of Line Crosses:

Group[1]	Alone	Social	Total
1	39.7(5.2)	148.9(12.8)	94.3(8.0)
2	97.6(17.9)	157.7(27.5)	127.7(21.9)
3	106.0(19.8)	133.8(27.7)	119.9(21.3)
4	121.3(18.3)	156.0(18.5)	138.7(17.3)
5	158.0(11.2)	210.0(18.5)	184.0(13.7)
6	159.7(20.2)	190.3(19.6)	175.0(18.8)

Number of Line Crosses Per Minute of Locomote:

Group	Alone	Social	Total
1	49.8(5.3)	97.5(3.4)	73.7(3.6)
2	63.2(6.3)	76.7(7.8)	69.9(6.9)
3	73.8(16.5)	69.7(8.6)	71.7(11.5)
4	76.9(9.7)	82.9(8.3)	79.9(8.8)
5	104.6(11.4)	97.4(5.8)	101.0(8.4)
6	101.4(10.1)	94.5(6.0)	98.0(7.5)

Interval Between Consecutive Line Crosses:

Group	Alone	Social	Total
1	0.90(.04)	0.62(.02)	0.76(.03)
2	1.13(.13)	0.93(.13)	1.03(.13)
3	1.16(.12)	1.02(.12)	1.09(.12)
4	0.95(.11)	0.85(.10)	0.90(.10)
5	0.70(.07)	0.69(.04)	0.69(.05)
6	0.76(.07)	0.73(.07)	0.74(.06)

[1] group 1 = saline control
group 2 = saline-Apo(5mg/kg)
group 3 = p-CPA(400mg/kg)/Apo(5mg/kg)
group 4 = p-CPA(250mg/kg)/Apo(5mg/kg)
group 5 = p-CA(10.4mg/kg)/Apo(5mg/kg)
group 6 = p-CA(6.4mg/kg)/Apo(5mg/kg)

Table 15
Means (and SEM) of TOTAL JUMP of the Six Groups In ALONE, SOCIAL, and TOTAL Trials

Group[1]	Alone	Social	Total
1	0	0	0
2	0.13(0.13)	1.80(1.40)	0.95(0.74)
3	0.33(0.30)	2.70(0.83)	1.50(0.49)
4	0.43(0.24)	4.20(2.00)	2.30(1.10)
5	3.10(2.10)	5.70(2.60)	4.40(2.30)
6	7.00(3.40)	9.30(3.10)	8.20(3.20)

[1] group 1 = saline control
group 2 = saline-Apo(5mg/kg)
group 3 = p-CPA(400mg/kg-Apo(5mg/kg)
group 4 = p-CPA(250mg/kg-Apo(5mg/kg)
group 5 = p-CA(10.4mg/kg-Apo(5mg/kg)
group 6 = p-CA(6.4mg/kg-Apo(5mg/kg)

Table 16
Means (and SEM) of the Dependent measures of the Social Behaviors of the Six Groups in SOCIAL trials

EVENT COUNT:

	Behavior				
Gr[1]	Allogroom	Aggress	Submit	Allosniff	Composite[2]
1	13.90(3.10)	1.80(.79)	5.50(.86)	29.00(3.10)	50.50(6.50)
2	0.27(0.12)	0.07(.04)	1.50(.59)	1.50(0.62)	3.30(1.30)
3	0.30(0.15)	0.13(.10)	1.40(.44)	0.73(0.31)	2.60(0.59)
4	0.33(0.26)	0.03(.03)	1.60(.46)	1.50(1.10)	3.40(1.70)
5	0.33(0.17)	0.17(.11)	2.00(.65)	0.70(0.22)	3.20(0.87)
6	0.33(0.23)	0.23(.17)	1.50(.48)	0.63(0.34)	2.70(0.99)

EVENT DURATION(seconds):

	Behavior				
Gr	Allogroom	Aggress	Submit	Allosniff	Composite
1	2.71(.51)	1.06(.41)	2.37(.41)	1.72(.12)	2.27(.15)
2	0.30(.16)	%[3]	0.69(.30)	0.27(.12)	0.57(.22)
3	0.37(.20)	%	0.63(.23)	0.23(.12)	0.73(.23)
4	0.60(.06)	%	1.34(.33)	0.70(.05)	1.40(.31)
5	0.16(.12)	%	1.00(.33)	0.21(.10)	0.95(.28)
6	0.19(.13)	0.15(.05)	1.53(.35)	0.21(.18)	1.48(.33)

DURATION PROBABILITY:

	Behavior				
Gr	Allogroom	Aggress	Submit	Allosniff	Composite
1	.110(.020)	.010(.005)	.040(.009)	.130(.010)	.290(.030)
2	.002(.001)	<.001	.009(.006)	.005(.002)	.020(.008)
3	.003(.002)	<.001	.010(.005)	.002(.001)	.020(.005)
4	.001(.001)	<.001	.010(.003)	.005(.005)	.020(.008)
5	.001(.001)	<.001	.020(.007)	.002(.001)	.020(.008)
6	.001(.001)	.001(.002)	.010(.003)	.001(.001)	.010(.004)

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[1] group 1 = saline control
group 2 = saline-Apo(5mg/kg)

group 3 = p-CPA(400mg/kg)/Apo(5mg/kg)
group 4 = p-CPA(250mg/kg)/Apo(5mg/kg)
group 5 = p-CA(10.4mg/kg)/Apo(5mg/kg)
group 6 = p-CA(6.4mg/kg)/Apo(5mg/kg)

[2] Composite = Allogroom+Aggress+Submit+Allosniff

[3] Event Duration not calculated when total duration was less than 0.5sec. in any one trial.

VIII. APPENDIX B : ANOVA Tables

Table 1
ANOVA Table for the Dependent Measures of LOCOMOTE

EVENT COUNT:

Source	df	MS	F	p
G (group)	5	3952.75	1.93	ns
Sw (subject)	54	2052.93		
C (condition)	1	36582.51	85.08	<.001
GXC	5	2572.50	5.98	<.001
CSw	54	429.99		

EVENT DURATION:

Source	df	MS	F	p
G (group)	5	8.72	6.72	<.001
Sw (subject)	54	1.30		
C (condition)	1	2.77	12.92	<.001
GXC	5	0.80	3.74	<.001
CSw	54	0.21		

DURATION PROBALILITY:

Source	df	MS	F	p
G (group)	5	1763.80	3.66	<.006
Sw (subject)	54	482.11		
C (condition)	1	3940.24	61.85	<.001
GXC	5	464.38	7.29	<.001
CSw	54	63.71		

Table 2
ANOVA Table for the Dependent Measures of REAR

EVENT COUNT:

Source	df	MS	F	p
G (group)	5	277.12	0.77	ns
Sw (subject)	54	358.52		
C (condition)	1	442.23	16.32	<.001
GXC	5	21.58	0.80	ns
CSw	54	27.11		

EVENT DURATION:

Source	df	MS	F	p
G (group)	5	177.68	2.02	ns
Sw (subject)	54	87.79		
C (condition)	1	0.01	0.001	ns
GXC	5	15.32	1.62	ns
CSw	54	9.44		

DURATION PROBALILITY:

Source	df	MS	F	p
G (group)	5	2439.83	1.86	ns
Sw (subject)	54	1309.85		
C (condition)	1	18.67	0.36	ns
GXC	5	78.26	1.53	ns
CSw	54	51.24		

Table 3

ANOVA TABLE for the Dependent Measures of SNIFF

EVENT COUNT:

Source	df	MS	F	p
G (group)	5	4384.98	2.10	ns
Sw (subject)	54	2086.00		
C (condition)	1	8604.45	42.43	<.001
GXC	5	374.29	1.85	ns
CSw	54	202.81		

EVENT DURATION:

Source	df	MS	F	p
G (group)	5	74.33	9.95	<.001
Sw (subject)	54	7.47		
C (condition)	1	18.11	4.56	<.037
GXC	5	80.11	20.16	<.001
CSw	54	3.97		

DURATION PROBALILITY:

Source	df	MS	F	p
G (group)	5	5620.41	5.80	<.001
Sw (subject)	54	969.52		
C (condition)	1	418.16	2.65	ns
GXC	5	1753.02	11.09	<.001
CSw	54	158.10		

Table 4
ANOVA Table for the Dependent Measures of INACTIVE

EVENT COUNT:

Source	df	MS	F	p
G (group)	5	182.94	34.09	<.001
Sw (subject)	54	5.37		
C (condition)	1	164.03	31.03	<.001
GXC	5	175.60	33.22	<.001
CSw	54	5.29		

EVENT DURATION:

Source	df	MS	F	p
G (group)	5	169.11	19.53	<.001
Sw (subject)	54	8.66		
C (condition)	1	141.52	15.52	<.001
GXC	5	168.45	18.47	<.001
CSw	54	9.12		

DURATION PROBALILITY:

Source	df	MS	F	p
G (group)	5	1360.38	35.03	<.001
Sw (subject)	54	38.84		
C (condition)	1	1326.34	34.13	<.001
GXC	5	1354.16	34.85	<.001
CSw	54	38.86		

Table 5
ANOVA Table for the Dependent Measures of SELF-GROOM

EVENT COUNT:

Source	df	MS	F	p
G (group)	5	60.38	33.12	<.001
Sw (subject)	54	1.82		
C (condition)	1	0.63	0.26	ns
GXC	5	0.02	0.008	ns
CSw	54	2.42		

EVENT DURATION:

Source	df	MS	F	p
G (group)	5	594.81	15.62	<.001
Sw (subject)	54	38.08		
C (condition)	1	158.77	3.31	ns
GXC	5	249.42	5.20	<.001
CSw	54	47.94		

DURATION PROBALILITY:

Source	df	MS	F	p
G (group)	5	718.77	31.23	<.001
Sw (subject)	54	23.02		
C (condition)	1	161.34	4.39	<.041
GXC	5	198.85	5.41	<.001
CSw	54	36.73		

Table 6
ANOVA Table for the Dependent Measures of HEAD-DOWN

EVENT COUNT:

Source	df	MS	F	p
G (group)	5	7506.15	6.13	<.001
Sw (subject)	54	1224.78		
C (condition)	1	4181.99	27.10	<.001
GXC	5	329.20	2.13	ns
CSw	54	154.33		

EVENT DURATION:

Source	df	MS	F	p
G (group)	5	32.52	7.64	<.001
Sw (subject)	54	4.26		
C (condition)	1	26.30	17.77	<.001
GXC	5	1.30	0.88	ns
CSw	54	47.94		

DURATION PROBALILITY:

Source	df	MS	F	p
G (group)	5	2838.22	5.92	<.001
Sw (subject)	54	479.31		
C (condition)	1	6725.35	68.19	<.001
GXC	5	363.63	3.69	<.006
CSw	54	98.63		

Table 7
ANOVA Table for the Dependent Measures of NOD

EVENT COUNT:

Source	df	MS	F	p
G (group)	5	656.13	1.17	ns
Sw (subject)	54	561.61		
C (condition)	1	27.23	0.47	ns
GXC	5	103.99	1.79	ns
CSw	54	57.96		

EVENT DURATION:

Source	df	MS	F	p
G (group)	5	58.81	2.20	ns
Sw (subject)	54	26.79		
C (condition)	1	4.81	3.52	ns
GXC	5	1.64	1.20	ns
CSw	54	1.37		

DURATION PROBALILITY:

Source	df	MS	F	p
G (group)	5	1842.30	1.96	ns
Sw (subject)	54	938.84		
C (condition)	1	308.03	5.80	<.020
GXC	5	46.14	0.87	ns
CSw	54	53.15		

Table 8
ANOVA Table for the Dependent Measures of GNAW

EVENT COUNT:

Source	df	MS	F	p
G (group)	5	255.00	1.62	ns
Sw (subject)	54	157.63		
C (condition)	1	1.23	0.08	ns
GXC	5	10.98	0.69	ns
CSw	54	15.97		

EVENT DURATION:

Source	df	MS	F	p
G (group)	5	239.03	1.75	ns
Sw (subject)	54	136.62		
C (condition)	1	17.84	1.42	ns
GXC	5	19.88	1.58	ns
CSw	54	12.61		

DURATION PROBALILITY:

Source	df	MS	F	p
G (group)	5	2458.49	2.10	ns
Sw (subject)	54	1169.46		
C (condition)	1	15.63	0.57	ns
GXC	5	35.25	1.29	ns
CSw	54	27.42		

Table 9
ANOVA Table for the Dependent Measures of REAR-GNAW

EVENT COUNT:

Source	df	MS	F	p
G (group)	5	8.19	1.10	ns
Sw (subject)	54	7.43		
C (condition)	1	0.03	0.04	ns
GXC	5	0.82	1.34	ns
CSw	54	0.61		

EVENT DURATION:

Source	df	MS	F	p
G (group)	5	182.00	1.93	ns
Sw (subject)	54	94.19		
C (condition)	1	4.19	0.88	ns
GXC	5	11.06	2.33	<.054
CSw	54	4.74		

DURATION PROBALILITY:

Source	df	MS	F	p
G (group)	5	348.81	1.76	ns
Sw (subject)	54	198.61		
C (condition)	1	24.03	1.84	ns
GXC	5	27.43	2.10	ns
CSw	54	13.04		

Table 10
ANOVA Table for the Dependent Measures of JUMP

EVENT COUNT:

Source	df	MS	F	p
G (group)	5	265.80	3.19	<.014
Sw (subject)	54	83.42		
C (condition)	1	282.67	21.78	<.001
GXC	5	14.12	1.09	ns
CSw	54	12.98		

EVENT DURATION:

Source	df	MS	F	p
G (group)	5	0.81	3.23	<.013
Sw (subject)	54	0.25		
C (condition)	1	0.78	19.16	<.001
GXC	5	0.06	1.42	ns
CSw	54	0.04		

DURATION PROBALILITY:

Source	df	MS	F	p
G (group)	5	13.76	2.92	<.021
Sw (subject)	54	4.72		
C (condition)	1	5.38	9.98	<.003
GXC	5	0.50	0.94	ns
CSw	54	0.54		

Table 11
ANOVA Table for the Dependent Measures of GNAW+NOD

EVENT COUNT:

Source	df	MS	F	p
G (group)	5	1060.40	1.38	ns
Sw (subject)	54	770.64		
C (condition)	1	16.47	0.20	ns
GXC	5	117.82	1.41	ns
CSw	54	83.62		

EVENT DURATION:

Source	df	MS	F	p
G (group)	5	230.15	1.49	ns
Sw (subject)	54	154.28		
C (condition)	1	41.64	3.12	ns
GXC	5	15.41	1.16	ns
CSw	54	13.33		

DURATION PROBALILITY:

Source	df	MS	F	p
G (group)	5	3525.28	1.71	ns
Sw (subject)	54	2064.13		
C (condition)	1	485.35	6.08	<.017
GXC	5	120.70	1.51	ns
CSw	54	79.81		

Table 12
ANOVA Table for the Dependent Measures of GNAW+REAR-GNAW

EVENT COUNT:

Source	df	MS	F	p
G (group)	5	269.81	1.54	ns
Sw (subject)	54	174.79		
C (condition)	1	0.90	0.05	ns
GXC	5	14.49	0.76	ns
CSw	54	19.06		

EVENT DURATION:

Source	df	MS	F	p
G (group)	5	259.18	1.64	ns
Sw (subject)	54	158.35		
C (condition)	1	35.64	2.58	ns
GXC	5	16.28	1.18	ns
CSw	54	13.81		

DURATION PROBALILITY:

Source	df	MS	F	p
G (group)	5	2504.17	1.76	ns
Sw (subject)	54	1425.77		
C (condition)	1	78.40	2.53	ns
GXC	5	32.77	1.06	ns
CSw	54	30.98		

Table 13

ANOVA Table for the Dependent Measures of COMPOSITE STEREOTYPY[1]

EVENT COUNT:

Source	df	MS	F	p
G (group)	5	1181.55	1.49	ns
Sw (subject)	54	793.17		
C (condition)	1	17.78	0.20	ns
GXC	5	114.28	1.31	ns
CSw	54	87.12		

EVENT DURATION:

Source	df	MS	F	p
G (group)	5	277.66	1.70	ns
Sw (subject)	54	163.84		
C (condition)	1	60.08	4.26	<.044
GXC	5	16.67	1.18	ns
CSw	54	14.12		

DURATION PROBALILITY:

Source	df	MS	F	p
G (group)	5	4978.19	2.28	ns
Sw (subject)	54	2183.74		
C (condition)	1	725.35	8.83	<.004
GXC	5	78.00	0.95	ns
CSw	54	82.19		

[1] Composite = Allogroom+Aggress+Submit+Allosniff

Table 14
ANOVA Table for the Additional Measures of LOCOMOTE

Number of Line Crosses:

Source	df	MS	F	p
G (group)	5	69667.88	3.79	<.005
Sw (subject)	54	18399.35		
C (condition)	1	247275.69	71.76	<.001
GXC	5	14042.50	4.08	<.003
CSw	54	3445.74		

Number of Line Crosses Per Minute of Locomote:

Source	df	MS	F	p
G (group)	5	11273.88	2.84	<.024
Sw (subject)	54	3970.00		
C (condition)	1	6007.50	7.72	<.007
GXC	5	6616.25	8.50	<.001
CSw	54	778.07		

Interval Between Consecutive Line Crosses:

Source	df	MS	F	p
G (group)	5	1.60	3.29	<.011
Sw (subject)	54	0.49		
C (condition)	1	1.48	44.32	<.001
GXC	5	0.16	4.88	<.001
CSw	54	0.03		

Table 15
ANOVA Table for TOTAL JUMP

Source	df	MS	F	p
G (group)	5	533.77	3.08	<.016
Sw (subject)	54	173.14		
C (condition)	1	403.23	21.12	<.001
GXC	5	23.63	1.24	ns
CSw	54	19.09		

Table 16
ANOVA Table for the Dependent Measures of ALLOGROOM

EVENT COUNT:

Source	df	MS	F	p
G (group)	5	923.01	19.33	<.001
Sw (subject)	54	47.76		
T (trial)	2	29.04	3.09	<.049
TXC	10	50.82	5.41	<.001
TSw	108	9.39		

EVENT DURATION:

Source	df	MS	F	p
G (group)	5	31.48	17.37	<.001
Sw (subject)	54	1.81		
T (trial)	2	14.64	12.39	<.001
TXC	10	1.33	1.13	ns
TSw	108	1.18		

DURATION PROBALILITY:

Source	df	MS	F	p
G (group)	5	605.08	22.15	<.001
Sw (subject)	54	27.32		
T (trial)	2	21.65	3.41	<.037
TXC	10	8.23	1.30	ns
TSw	108	6.35		

Table 17
ANOVA Table for the Dependent Measures of AGGRESS

EVENT COUNT:

Source	df	MS	F	p
G (group)	5	14.15	4.14	<.003
Sw (subject)	54	3.42		
T (trial)	2	0.84	0.98	ns
TXC	10	2.75	3.19	<.001
TSw	108	0.86		

EVENT DURATION:

Source	df	MS	F	p
G (group)	5	5.38	6.08	<.001
Sw (subject)	54	0.88		
T (trial)	2	2.01	1.82	ns
TXC	10	1.88	1.70	ns
TSw	108	1.11		

DURATION PROBALILITY:

Source	df	MS	F	p
G (group)	5	6.60	4.92	<.001
Sw (subject)	54	1.34		
T (trial)	2	1.67	4.45	ns
TXC	10	1.91	1.66	ns
TSw	108	1.15		

Table 18
ANOVA Table for the Dependent Measures of SUBMIT

EVENT COUNT:

Source	df	MS	F	p
G (group)	5	75.72	7.06	<.001
Sw (subject)	54	10.73		
T (trial)	2	25.35	3.79	<.026
TXC	10	17.04	2.55	<.009
TSw	108	6.69		

EVENT DURATION:

Source	df	MS	F	p
G (group)	5	12.67	3.93	<.004
Sw (subject)	54	3.23		
T (trial)	2	7.82	2.67	ns
TXC	10	1.73	0.59	ns
TSw	108	2.93		

DURATION PROBALILITY:

Source	df	MS	F	p
G (group)	5	46.98	4.82	<.001
Sw (subject)	54	9.74		
T (trial)	2	35.36	5.95	<.004
TXC	10	10.60	1.78	ns
TSw	108	5.94		

Table 19
ANOVA Table for the Dependent Measures of ALLOSNIFF

EVENT COUNT:

Source	df	MS	F	p
G (group)	5	3932.05	70.67	<.001
Sw (subject)	54	55.64		
T (trial)	2	79.57	3.75	<.027
TXC	10	160.05	7.54	<.001
TSw	108	21.23		

EVENT DURATION:

Source	df	MS	F	p
G (group)	5	11.71	26.20	<.001
Sw (subject)	54	0.45		
T (trial)	2	2.31	7.18	<.001
TXC	10	0.35	1.10	ns
TSw	108	0.32		

DURATION PROBALILITY:

Source	df	MS	F	p
G (group)	5	797.82	98.86	<.001
Sw (subject)	54	8.07		
T (trial)	2	6.49	1.35	ns
TXC	10	9.29	1.93	<.048
TSw	108	4.80		

Table 20

ANOVA Table for the Dependent Measures of COMPOSITE SOCIAL[1]

EVENT COUNT:

Source	df	MS	F	p
G (group)	5	11275.20	46.80	<.001
Sw (subject)	54	240.90		
T (trial)	2	115.27	2.09	ns
TXC	10	398.33	7.22	<.001
TSw	108	55.20		

EVENT DURATION:

Source	df	MS	F	p
G (group)	5	11.58	5.61	<.001
Sw (subject)	54	2.07		
T (trial)	2	12.08	4.88	<.009
TXC	10	1.67	0.67	ns
TSw	108	2.48		

DURATION PROBALILITY:

Source	df	MS	F	p
G (group)	5	3848.68	57.53	<.001
Sw (subject)	54	66.90		
T (trial)	2	105.00	4.87	<.009
TXC	10	13.15	0.61	ns
TSw	108	21.55		

[1] Composite = Allogroom+Aggress+Submit+Allosniff

IX. APPENDIX C : Tables of Reliability Measures

Table 1
Agreement Matrix for Kappa Coefficient Test-Retest

		Test 1					
	Behaviors[1]	Q	W	G	T	Y	pi1[2]
Test2	Q	11		1			12/120=.100
	W		5				5/120=.042
	G	4		74		1	80/120=.667
	T			1	4		5/120=.042
	Y			1		18	9/120=.158
pi2		.125	.042	.642	.033	.158	

Po=112/120=0.933 ; Pc=0.469
Kappa=(0.933-0.469)/(1-0.469)=0.874

[1] Q=Locomote
W=Rear
G=Sniff
T=Self-groom
Y=Inactive

[2] pi1=Proportions of total entries for Test 1
pi2=Proportions of totol entries for Test 2

Po=Proportion of agreement
Pc=Proportion of chance agreement

Table 2

Agreement Matrix for Kappa Coefficient Interjudge

		Test 1					
	Behaviors[1]	Q	W	G	T	Y	pi1[2]
	Q	12		3			15/120=.125
	W		5	3			8/120=.067
Test2	G	3		68	2	2	75/120=.625
	T				2		2/120=.017
	Y			3		17	20/120=.167
pi2		.125	.042	.642	.033	.158	

Po=104/120=0.867 ; Pc=0.447
Kappa=(0.867-0.447)/(1-0.447)=0.759

[1] Q=Locomote
W=Rear
G=Sniff
T=Self-groom
Y=Inactive

[2] pi1=Proportions of total entries for Test 1
pi2=Proportions of totol entries for Test 2

Po=Proportion of agreement
Pc=Proportion of chance agreement

Table 3
Correlation[1] Matrix for Behaviors of a Normal Rat Test-Retest and Interjudge Trials

	Test 1	Test 2	Interjudge
Test 1	1.0000		
Test 2	0.9981	1.0000	
Interjudge	0.9991	0.9961	1.0000

Correlation[1] Matrix for Behaviors of a Drugged[2] Rat Test-Retest and Interjudge Trials

	Test 1	Test 2	Interjudge
Test 1	1.0000		
Test 2	0.9999	1.0000	
Interjudge	0.9993	0.9997	1.0000

[1] Correlation calculated on agreement across all behaviors coded. Dependent measure was Duration Probability

[2] Drug used was d-amphetamine(2mg/kg)